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A NEW PREPARATION FOR THE STUDY OF EXPERIMENTAL SHOCK FROM MASSIVE WOUNDS

I. STANDARDIZATION

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PURPOSE

IN World War I, World War II, and in the Korean Conflict a certain number of casualties with massive soft tissue wounds died in spite of competent, energetic, and sometimes heroic medical care.

Even though adequate hemostasis had been effected and blood volumes restored, many of these patients succumbed to a shock state which could not be reversed by whole blood replacement. Ziperman,[1] in a statistical survey of the causes of shock in the Korean war zone, listed soft tissue injury, especially in the gluteal area, as a common cause of hypotensive states in casualties.

Opportunity to observe clinical traumatic shock between wars is extremely limited. In order to study the problem of massive wounding, an experimental preparation was developed at these laboratories which closely simulates the problem as encountered on the battlefield. Information thus derived could also be applied to the problem of the treatment of massive civilian casualties in nuclear warfare.

MATERIAL AND METHODS

Experimental Animal.—The goat was used in these studies. Its relative availability, docility, large size approximating that of a small man, and its

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sturdiness were considered in this selection. The Texas angora wether (castrated male), 4 to 5 years of age, was chosen for the standard wound shock preparation over other breeds and sexes, since it proved to be healthier and more uniform in its response to injury.

Upon arrival, all animals were given routine inoculations of hemorrhagic septicemia bacterin (Lederle) and kept under observation for a period of not less than 2 weeks or more than 6 weeks prior to experimental use. Only healthy animals weighing between 36.4 and 54.6 kilograms were utilized in these experiments.

On the night preceding injury, the animal was shorn over the area to be traumatized and weighed. Food and water were withheld for 12 hours before injury.

Technique of Injury.—The animals were placed on a special experimental table and injury was produced by detonation of cylindrical tetryl pellets (0.494 by 0.795 inches) placed on a predetermined site on both hindquarters. This target point was on a line one-quarter of the distance from the knee to the greater trochanter of the femur and at the midpoint of the muscle mass along that line. The size of the charge was carefully selected so that the detonation would produce approximately 100 per cent soft tissue damage from the pelvic brim downward. The wounds were remarkably uniform. Both femurs were comminuted, and all muscle groups were severed on the anterior, lateral, and posterior aspects of the thigh. The muscle bellies and connective tissue proximal to the point of detonation exhibited small areas of gross hemorrhage and petechial-like areas of injury up to the pelvic brim. The vessels were severed and thrombosed by the detonation. Intrapelvic and intraperitoneal damage was limited to a few small petechiae on loops of small bowel, cecum, and on urinary bladder serosa.

Hemostasis was effected within minutes of injury by clamping obvious bleeding points. The generalized muscle ooze was controlled by loose packing of the wound with sterile cotton gauze bandage. The dressing was completed by enclosing both limbs in a section of sterile 6-inch stockinette. A plastic sheet was then placed over the dressing, clamped beneath the anus, and pinned over the skin of the pelvis to prevent direct fecal contamination of the wound.

During the survival period, the animals were kept in a constant temperature laboratory. Beginning 6 hours postinjury, the animals were given food and water, ad libitum. The initial blood loss was designated as that blood loss into a pan prior to the application of dressing. This loss was measured in a graduated flask. Subsequent blood loss was estimated by bandage weight techniques. The total blood loss was obtained by adding 100 c.c. to the sum of these 2 measured blood losses. This figure of a 100 c.c. was judged more than adequate to allow for loss on hands and clothing.

RESULTS

Prewounding Factor.—The final experimental preparation was perfected only after a period of extensive standardization in which various factors were evaluated such as the influence of breed, sex, age, geographic source, external

temperature, and body temperature. None of the aforementioned factors had any significant influence on the survival time of these animals. Of special interest among the prewounding factors studied was the lack of correlation between initial hemoglobin (Fig. 1) and survival time. In addition, there was no demonstrable correlation between survival time and blood loss provided the initial blood loss did not exceed 15 c.c. per kilogram of body weight (Figs. 2 and 3).*

Survival Time of Control Animals.—A total of 96 animals were used in the control group. Mean survival time for this group was 18.9 hours ± 0.98 hours. No significant variations were noted to occur between separate groups of animals in the course of the experiment. As a consequence the individual control groups were consolidated in the final statistical evaluation. It should be noted that all animals died as a result of the wounds inflicted. Animals in which the initial blood loss exceeded 15 c.c. per kilogram of body weight were discarded from the analysis, since it was demonstrated that in this range survival time was not independent of blood loss, as previously mentioned. Nevertheless, it is possible that certain of the early-dying animals included in the study succumbed to exsanguination into their wounds without manifesting increased external blood loss.

TABLE I

POSTWOUNDING FACTORS	NUMBER OF ANIMALS	MEAN SURVIVAL TIME	S.E.M.	P*
1. Wound dressing				
A. No dressing	11	18.2	±3.2	N.S.
B. Pressure dressing	10	24.7	±2.1	0.02
2. Position change	10	12.2	±9.3	0.05
3. Physiologic factors				
A. Venous sampling only	50	12.5	±1.3	0.01
B. Direct blood pressure measurements	18	11.8	±1.9	0.01
C. Direct blood pressure measurements and venous sampling	29	11.3	±2.0	0.01
4. Aseptic precautions	10	26.4	±2.1	0.05
5. Control animals	96	18.9	±0.9	-

*P values were determined by the *t* test based on the difference between control animals and other groups.
N.S.—Not significant ($P > 0.05$).

Postwounding Factors (Table I).—

Dressings: It was demonstrated that loose dressings as employed in the standard preparation had no advantage over the omission of all dressing as gauged by survival of the animal. The application of pressure dressing, however, did prolong survival time to 24.7 hours.

*Range of initial external blood loss, 60 to 560 c.c.; range of total external blood loss, 440 to 1,480 c.c.

Fig. 1.

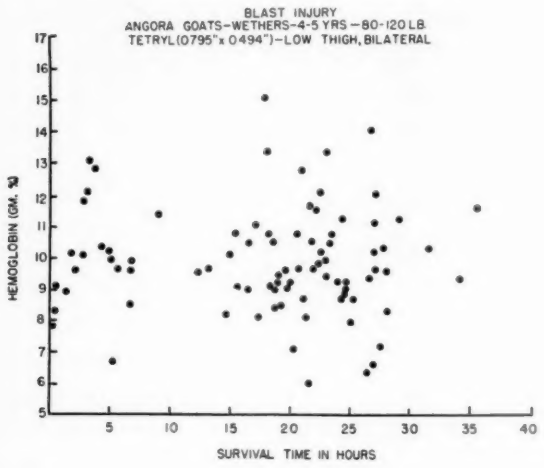

Fig. 2.

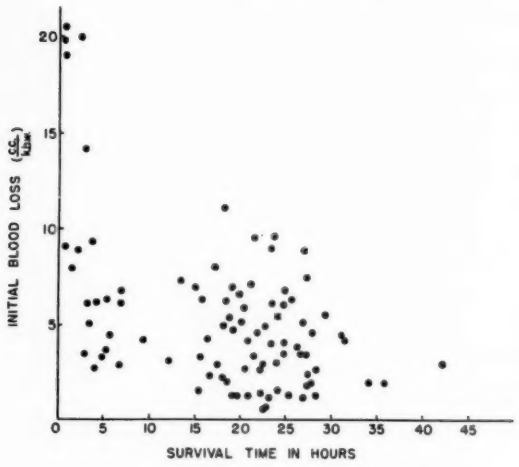

Fig. 3.

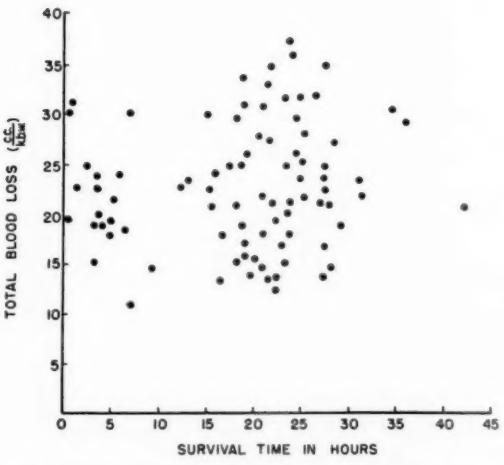

Fig. 1.—Each dot represents the initial hemoglobin determination in a control animal. This scattergram illustrates the lack of correlation between prewounding hemoglobin and survival time.

Fig. 2.—Each dot represents the immediate postwounding external blood loss in a single control animal. Note lack of correlation between initial external blood loss and survival time.

Fig. 3.—Each dot represents the total measured external blood loss in a single control animal after wound. Note lack of correlation between total measured external blood loss and survival time.

Positional change: Completely turning the animal from the prone to the supine position for 5 minutes and back again every fourth hour during the postinjury period significantly decreased the survival time. Most of the animals died shortly after one of the periods of positional change.

Effect of physiologic studies: The effect of manipulations necessitated by physiologic studies had a profound influence in shortening the survival time. Reference to Table I suggests that the degree of reduction seems to be approximately proportional to the amount of manipulation performed. Because of this disclosure, all subsequent survival studies were completely divorced from simultaneous physiologic determinations.

Aseptic precautions: The use of surgically accepted aseptic techniques resulted in significant prolongation of survival time. These techniques included (1) depilation with strontium sulfide in the target area, (2) cleansing with hexachlorophine, (3) draping the carts and animals with sterile sheets, (4) the use of sterile clamps for hemostasis, and (5) employment of caps, masks, sterile gowns, and sterile gloves by the experimenters. Although it was felt that this procedure reduced the initial wound inoculum of bacteria, the nature of the experimental procedures made complete asepsis impossible.

SUMMARY

1. A new experimental preparation for the study of massive soft tissue trauma is described. Although we recognize that this preparation incorporates more variables than the usual experimental shock preparation, it is felt that there are distinct advantages inherent in its similarity to battlefield or civilian mechanical traumatic injuries.

2. Survival studies have been completely divorced from physiologic studies, and the reasons for this separation have been discussed.

3. The lack of demonstrable correlation between blood loss and survival time in the injured animal suggests that death is not entirely due to exsanguination.

4. That a bacterial factor may be involved in some way in the death of the traumatized animals is suggested by the fact that observance of aseptic techniques before and after injury significantly prolonged mean survival.

REFERENCE

1. Ziperman, H. H.: The Management of Large Bowel Injuries in the Korean Campaign, U. S. Armed Forces Med. J. 7: 85-91, 1956.

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A NEW PREPARATION FOR THE STUDY OF EXPERIMENTAL SHOCK FROM MASSIVE WOUNDS

II. Evaluation of Various Therapeutic Regimens With Special Reference to the Role of Antibiotics, Fluid Replacement, and Débridement

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SYSTEMIC TREATMENT OF SHOCK FROM MASSIVE WOUNDS

THE phenomenon of irreversible shock in human beings is seen chiefly in shock due to burns, in some cases of massive tissue injury, in still fewer persons with prolonged shock from hemorrhage, and in some cases of sepsis for which there is no definite antibiotic therapy. The present interests of these laboratories are directed toward shock from massive wounds. For purposes of studying this entity, a standard wound shock preparation was developed and standardized by Ochsner and associates.[10] The purpose of this series of experiments was to evaluate available forms of therapy and to establish a perimeter of knowledge from which protocol for further basic studies might originate.

In this group of studies variables were confined (insofar as possible) to methods of therapy. Concomitant physiologic studies were kept to a minimum since it was previously established[10] that relatively minor manipulation (that is, blood sampling for chemistries and direct arterial blood pressure measurements) significantly reduced survival times.

EXPERIMENTAL ANIMAL AND BASIC ROUTINE

All animals used in these experiments were Angora wether goats (Texas), 4 to 5 years of age and weighing 80 to 120 pounds (36.4 to 56.6 Kg.). Food and water were withheld for 12 hours prior to injury. Shock was produced by blast injury technique, as described in a previous report,[10] using the standard tetryl pellet (0.795 by 0.494 inch) and M36 detonator cap. The tetryl charges were placed on a horizontal line one-fourth of the distance from the knee to the greater trochanter and at the midpoint of the hindquarter muscle mass along that line. Charges were detonated bilaterally. Hemostasis was affected following injury by clamping all grossly bleeding vessels. Sterile, loose, dry

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dressings were applied to all wounds. The external blood loss* was measured by techniques described in a previous report.[10] All animals were offered food and water ad libitum beginning 6 hours postinjury.

Therapy was separated into the following general groups: (1) treatment by fluid replacement, (2) treatment with antibiotics, (3) treatment with fluid replacement plus antibiotics, and (4) treatment with fluids, antibiotics, and wound débridement.

CONTROL ANIMALS

The control groups of animals have been consolidated for purposes of statistical analysis. The mean survival time for the consolidated control group was 19.6 hours (Table I). Where statistical comparisons were made between control versus treatment groups, a probability value of 0.05 was considered as the upper limit of statistical significance.

TABLE I. TREATMENT WITH FLUIDS ONLY

TREATMENT	NUMBER OF ANIMALS	SURVIVAL TIME IN HOURS	S. E. M.	P*
A. Consolidated controls	117	19.6	0.526	- -
B. Blood alone				
1. 1,000 c.c. in excess of total external blood loss	10	36.4	1.94	0.01
2. 500 c.c. in excess of 2-hour external blood loss	10	29.6	3.652	0.01
C. Blood plus dextran				
1. 1,000 c.c. dextran, whole blood equal to total external blood loss	10	23.6	1.668	0.02
2. To maintain normotensive blood pressure	10	21.3	4.20	N.S.
D. Dextran alone				
1. 500 c.c. in excess of 2-hour external blood loss	10	16.1	1.52	0.05

*P compared to consolidated control groups of animals.
N.S.—Not significant.

TREATMENT BY FLUID REPLACEMENT

Methods.—Fifty animals were treated after injury with whole blood alone, blood plus dextran, or with dextran alone. Aseptic precautions were observed when blood was drawn, and random cultures done periodically on donor blood were sterile. All blood was collected in 500 c.c. Transfuso-vac bottles (Baxter) in which 4 per cent sodium citrate (50 c.c.) was used as an anticoagulant. Each pint of whole blood was checked for hemolysis and crossmatched with the recipient animal before administration. A commercial preparation of 6 per cent dextran† (molecular weight 25,000 to 200,000) was used in these experiments. Sterile plastic, disposable, recipient sets were used for the administration of blood and dextran. In all fluid replacement experiments treatment was started within one-half hour following injury.

*Range of initial external blood loss in control animals, 40 to 714 c.c.; range of total external blood loss in control animals, 500 to 1,320 c.c.

†Manufactured by the J. T. Baker Chemical Company, Phillipsburg, N. J.

Ten animals were given at least 1,000 c.c. of whole blood in excess of the measured total external blood loss.* In another group of 10 animals, 500 c.c. in excess of the measured 2-hour external blood loss was given. In a series of 10 animals in which blood and dextran were administered, 1,000 c.c. of dextran given immediately after injury was followed by whole blood so that the total input of fluid was 1,000 c.c. in excess of the total external blood loss. Ten additional animals were given blood or blood plus dextran in sufficient quantity to maintain a normotensive arterial blood pressure. A final series of 10 animals were given 500 c.c. of dextran in excess of the measured 2-hour external blood loss.

Results.—Those animals which were given at least 1,000 c.c. of whole blood in excess of the measured total external blood loss survived a mean of 36.4 hours. When only 500 c.c. of whole blood in excess of the measured 2-hour external blood loss was given to 10 animals postinjury, the mean survival was 29.6 hours. In the group of animals which were given 1,000 c.c. of dextran followed by whole blood so that the total input was 1,000 c.c. in excess of the total measured external blood loss, the mean survival time was 23.8 hours. Where the maintenance of a normotensive arterial blood pressure was the criterion for the administration of blood or dextran plus blood, the animals survived a mean of 21.3 hours, an increase in survival time which is not statistically significant. Animals treated with 500 c.c. of dextran in excess of the measured 2-hour blood loss survived for a mean of 16.1 hours, a decrease in survival time which is statistically significant. (Table I.)

TREATMENT WITH ANTIBIOTICS ONLY

Parenteral Antibiotic Therapy.—

Methods: Fifty-two animals were treated with penicillin. Animals receiving penicillin were divided into 2 large treatment groups: (1) those treated by intravenous and intramuscular routes and (2) those treated only by intramuscular injection. Of the former group, 9 were treated before and immediately following injury. In another 9 animals treatment was begun immediately after injury and in 9 others therapy was withheld until 12 hours following injury. In the latter of the 2 major treatment groups, 10 animals were given procaine penicillin and 15 animals aqueous crystalline penicillin. Both of these subgroups were treated before and after injury. In all cases where penicillin was given, therapy, once instituted, was continued until death of the animal.

All animals treated with intramuscular and intravenous penicillin were given identical dosages, that is, 1,000,000 units of crystalline penicillin for the initial intravenous dose followed by 200,000 units of crystalline penicillin intravenously every 4 hours and 300,000 units of long-acting penicillin (procaine penicillin or penicillin in oil) initially and 300,000 units every 8 hours intramuscularly.

Two groups of animals were treated by the intramuscular injection of penicillin only. Time schedules for initiation of therapy and subsequent doses

*Amount of blood given in excess of total measured external blood loss varied between 1,500 and 2,000 c.c.

administered were identical for both groups. The type of penicillin given the animals was varied; one group received procaine penicillin and the other group aqueous crystalline penicillin.

Therapy in all other experimental groups treated with antibiotics was withheld until the immediate postinjury period.

Fifteen animals were given intramuscular dihydrostreptomycin in doses of 1 Gm. immediately postinjury and 1 Gm. every 12 hours until death.

Procaine penicillin (300,000 units every 6 hours) and dihydrostreptomycin (1 Gm. every 12 hours) intramuscularly were given to another group of 15 animals.

Sixteen animals were given 500 mg. of Aureomycin hydrochloride in 100 c.c. of saline intravenously every 6 hours during the period of survival.

A final series of 10 animals was given intravenous chloramphenicol. One gram was given immediately after injury and 500 mg. were administered every 6 hours until death of the animal.

Results: The results of systemic antibiotic therapy are tabulated in Table II. The mean survival time of animals treated with penicillin prior to and following injury is 55 hours. Delaying treatment until the immediate postinjury period did not significantly alter the mean survival time. However, a delay of 12 hours prior to the beginning of therapy lowered the mean survival time to 25 hours. When animals were treated by intramuscular injection of

TABLE II. TREATMENT WITH ANTIBIOTICS ONLY

TREATMENT	NUMBER OF ANIMALS	MEAN SURVIVAL TIME (HOURS)	S. E. M.	P*
I. *Parenteral antibiotic treatment*				
A. Consolidated controls	117	19.6	0.526	- -
B. Penicillin (I.M. and I.V.) continuous				
1. Pre- and postinjury	9	55.0	6.54	0.01
2. Postinjury†	9	54.3	12.05	0.01
3. Beginning 12 hours postinjury	7	25.0	3.98	N.S.
C. Penicillin (I.M. only) continuous				
1. Pre- and postinjury (procaine)	10	51.3	3.26	0.01
2. Pre- and postinjury (aqueous)	15	32.9	4.39	0.01
B. Dihydrostreptomycin (I.M.)				
1. Postinjury	15	18.3	1.92	N.S.
E. Dihydrostreptomycin and penicillin (I.M.)				
1. Postinjury	15	62.6	10.38	0.01
F. Aureomycin HCl (I.V.)				
1. Postinjury	16	66.8	6.71	0.01
G. Chloramphenicol (I.V.)				
1. Postinjury	10	63.6	10.12	0.01
II. *Oral antibiotic treatment*				
A. Aureomycin (P.O.)				
1. Pretreatment	10	39.1	7.75	0.02
B. Neomycin (P.O.)				
1. Pretreatment	7	15.2	4.96	N.S.
C. Aureomycin (P.O.)				
1. Immediate postinjury	9	21.2	5.31	N.S.

*P compared to consolidated control group of animals.
†All postinjury therapy begun immediately after wounding.
N.S.—Not significant.

penicillin, procaine penicillin was superior in effect to aqueous crystalline penicillin even though the dosage of the aqueous variety was somewhat higher. The mean survival times of these 2 groups of animals were 51.3 and 32.9 hours, respectively.

Fifteen animals treated with intramuscular dihydrostreptomycin showed no increase in survival times. However, when penicillin and dihydrostreptomycin were used in combination, the mean survival time was increased to 62.6 hours.

The mean survival times of animals treated with intravenous Aureomycin HCl and intravenous chloramphenicol were 66.8 and 63.6 hours, respectively.

With the exception of the streptomycin group and the penicillin group when treatment was begun 12 hours after injury, the increase in survival time of all animals treated by the intramuscular and/or the intravenous administration of antibiotics was statistically significant.

Oral Antibiotic Therapy.—

Methods: Twenty-six animals were treated with oral antibiotics. Ten were pretreated with 10 Gm. of Aureomycin daily (in divided doses) for 3 days prior to injury and were given a priming dose of 20 Gm. 5 hours before injury.

Seven animals were pretreated with 10 Gm. of neomycin daily (in divided doses) for 4 days prior to wounding and 20 Gm. of neomycin was given as a priming dose 5 hours before injury.

Nine animals were given oral Aureomycin beginning in the immediate postinjury period and continuing until the death of the animals. Four of these animals were given 5 Gm. of Aureomycin immediately after injury and 5 Gm. every 8 hours thereafter. The other 5 animals were given 10 Gm. doses of Aureomycin beginning immediately after injury and every 8 hours until the animals' death.

These astronomic doses of Aureomycin and neomycin were given because lower dosages were found to be ineffective in significantly reducing the fecal floral count.

Results: In the pretreatment groups neomycin was more effective in lowering the fecal bacterial count than was Aureomycin. The blood level of Aureomycin on the third treatment day varied between 2.5 and 5 micrograms per cubic centimeter of serum. Levels for neomycin were consistently zero. The mean survival time for animals pretreated with Aureomycin was 39.1 hours (a significant increase) while the mean survival time of animals pretreated with neomycin was 15.2 hours. The latter figure is not significantly different from the mean survival time of control animals.

In 9 animals where oral Aureomycin therapy was withheld until the immediate postinjury period, the mean survival time for the series was 21.2 hours.

TREATMENT WITH FLUID REPLACEMENT PLUS ANTIBIOTICS

Methods.—Fourteen animals were given penicillin and blood immediately postinjury. Blood was given so that the total amount transfused was at least

1,000 c.c. in excess of the measured total external blood loss. Procaine penicillin, 300,000 units every 6 hours, was given intramuscularly to this group of animals.

Another group of 10 animals was treated by transfusion therapy (in amounts comparable to the above) in combination with 500 mg. of Aureomycin administered intravenously every 6 hours beginning immediately following wounding and continuing until death of the animal.

Postinjury procaine penicillin (in dosage identical to those outlined above) and sufficient dextran to replace the measured 2-hour external blood loss were administered to 10 animals of another experimental series.

Ten animals received intramuscular penicillin and subcutaneous saline (by hypodermoclysis). Alidase was given with each hypodermoclysis to insure rapid absorption.

Five animals were given penicillin via the intramuscular route and dextran by hypodermoclysis. Again Alidase was used to facilitate absorption.

Results.—Where whole blood was used in combination with an antibiotic, a synergistic effect was observed (Table III). The mean survival times for those animals treated with penicillin and blood in combination was 98.6 hours. When compared to transfusion therapy alone where the mean survival time was 36.4 hours and to penicillin therapy alone with a mean survival time of 55 hours, the synergistic effect is rather striking. The mean survival times of animals treated with Aureomycin and blood transfusions in combination likewise shows an increase over the mean survival times of animals in which these agents were used individually as methods of therapy.

TABLE III. TREATMENT WITH FLUIDS AND ANTIBIOTICS

TREATMENT	NUMBER OF ANIMALS	MEAN SURVIVAL TIME (HOURS)	S. E. M.	P*
Consolidated controls	117	19.6	0.526	- -
Postinjury penicillin and blood	14	98.6	7.58	0.01
Postinjury Aureomycin and blood	10	71.0	7.55	0.01
Postinjury penicillin and dextran to replace 2-hour blood loss	10	18.5	3.81	N.S.
Penicillin and saline hypodermoclysis with Alidase	10	68.8	22.97	0.05
Penicillin and dextran hypodermoclysis with Alidase	5	42.5	8.54	0.02

*P compared to consolidated control groups of animals.
N.S.—Not significant.

In another group of 10 animals treated with penicillin (intramuscularly) and saline (by hypodermoclysis), the mean survival time is 68.8 hours. However, the standard deviation of this group is so large as to make interpretation of the data difficult. If one animal (No. 6499) which survived 250.5 hours following injury is excluded from the calculated mean, then the new mean survival time becomes 48.4 hours. This figure is not significantly different from the mean survival time of several groups of animals when penicillin alone was the therapy used.

When penicillin and intravenous dextran were combined as means of therapy, the resulting mean survival time of 21.2 hours is not significantly different from that of the consolidated control group of animals.

TREATMENT WITH FLUIDS, ANTIBIOTICS, AND WOUND DÉBRIDEMENT

Methods.—Eighty-four animals were treated by débridement and may be divided into 8 groups with reference to therapy as follows.

Series a: Seven uninjured animals were subjected to bilateral hip disarticulation. No penicillin therapy was given to this group of animals.

Series b: Twelve wounded animals were débrided at a mean time of 1.9 hours after injury. Penicillin was not administered to these animals.

Series c: In 5 uninjured animals bilateral hip disarticulation was followed by penicillin therapy.

Series d: In 15 wounded animals penicillin therapy was started immediately following injury and débridement begun after the intravenous administration of 2,000 c.c. of whole blood. The mean time between wounding and the beginning of surgery for this series of animals was 2.4 hours.

Series e: In 10 animals the initiation of therapy (penicillin and transfusion) was delayed for 6 hours postinjury. The mean time for the beginning of surgery in this group of animals was 8.8 hours.

Series f: Therapy (penicillin and transfusion) was withheld for 12 hours in 18 animals. Surgery was begun at a mean of 14.5 hours postinjury.

Series g: In 5 animals therapy was started immediately after wounding and débridement delayed for 24 hours.

Series h: In 6 animals therapy begun immediately after injury included not only penicillin and transfusion but also local cooling of the wounds. Débridement was delayed for 24 hours.

All animals of these groups were given sufficient blood to replace not only the measured total external blood loss due to trauma but also the measured operative blood loss. In the experiments in which animals were injured prior to surgery (series b, d, e, f, g, and h), all animals prior to surgery had received at least 1,000 c.c. of whole blood in excess of their external blood loss.

In experiments in which penicillin was given (series c, d, e, f, g, and h) 1,000,000 units of aqueous crystalline penicillin intravenously and 300,000 units of procaine penicillin intramuscularly were administered at the outset of therapy. In series g and h an additional 300,000 units of procaine penicillin was given via the intramuscular route every 6 hours for the 24-hour period prior to débridement. All penicillin-treated animals were given 300,000 units of procaine penicillin once daily after completion of surgery.

In series h local cooling was accomplished by the direct application of crushed ice to the open wounds. Local cooling was begun immediately after wounding.

Variables in anesthesia and methods of handling the amputation wounds with respect to closure are listed in Table IV.

TABLE IV

SERIES	NUMBER OF ANIMALS	ANESTHESIA	WOUND	COMMENT
a	7	1—Spinal 6—Local	All open	-
b	12	1—Spinal 11—Local	9 Open 2 Closed	1 animal sacrificed after attempt to reproduce convulsive seizure which occurred during surgery
c	6	1—Pentothal 2—Spinal 3—Local	3 Open 3 Closed	-
d	15	5—Spinal 10—Local	11 Open 3 Closed	1 animal had pulmonary edema and died during surgery
e	10	9—Local	9 Open	1 animal died prior to surgery
f	18	2—Spinal 12—Local	14 Open	4 animals died prior to treatment
g	5	5—Spinal	All closed	1 animal died prior to surgery
h	6	6—Spinal	All closed	-

With the exception of series h all animals in these groups were treated until death of the animal. In series h all animals except one were sacrificed at 14 days. This one animal was given intensive nursing care until death. The animals of this group were sacrificed at 14 days because it was felt that any animal living beyond 2 weeks after injury ultimately died of secondary causes which were mainly the result of poor nursing care.

Postoperative nursing care is difficult at best in the experimental animal. Because of the nature of the injury in this preparation and the extent of surgery necessary to adequately débride the wounds, postoperative ambulation was impossible. Attempts to rehabilitate these animals using an especially designed hindlimb carriage were unsuccessful. Confinement of the animal to the cart resulted in an undesirable immobility which increased the danger of local contamination of the wounds and enhanced decubitus ulcer formation. These 2 factors are undoubtedly of extreme importance in the death of the animal. For example, where amputation wounds are left open, secondary muscle infection is grossly evident after 36 to 48 hours. In the animal living longer than 7 days, an area of pressure necrosis with decubitus ulcer formation and secondary infection occurred over the presternal area. In many instances this was so extensive as to involve the periosteum of the sternum and underlying cortical bone.

Results.—The mean survival time of unwounded animals which were subjected to bilateral hip disarticulation and which were not given penicillin was 2.8 days. The longest living animal in this series survived for 6.9 days.

In the series of 12 animals which were wounded and the wounds débrided early in the postinjury period without benefit of penicillin therapy, the mean survival time was 2.2 days. The longest surviving animal of this group lived for 6.0 days.

In the group of unwounded animals which were given penicillin after bilateral hip disarticulation, the mean survival time was 15.3 days. The longest surviving animal of this series lived 32.4 days.

The mean survival time of 15 wounded animals treated with penicillin and débrided early in the postinjury period was 14.7 days. In this series, 36.0 days was the longest survival time of any animal.

When therapy (transfusion and penicillin) were delayed for 6 hours and débridement delayed for a mean of 8.8 hours after injury, the mean survival time was 4.0 days with the longest survivor living for 11.2 days.

In 16 animals in which the treatment delay was 12 hours and débridement delay was 14.5 hours after wounding, the mean survival time was 3.6 days. The longest surviving animal of this series lived for 12.1 days.

When treatment was started immediately after wounding and surgery delayed for 24 hours, the mean survival for the series was 7.7 days. The longest living animal of this series survived for 9.8 days.

In the group of 6 animals in which therapy was started immediately after wounding and included local cooling as a part of the treatment and in which surgery was delayed for 24 hours, all animals lived for and were sacrificed at 14 days except one which was permitted to live until death at 56 days postinjury.

The above data are summarized in Table V.

TABLE V. TREATMENT WITH FLUID REPLACEMENT, ANTIBIOTICS, AND DÉBRIDEMENT

SERIES	INJURY AND SURGERY	NUMBER OF ANIMALS	TRANSFUSED	PENICILLIN THERAPY	MEAN TIME BLOOD AND/OR PENICILLIN THERAPY STARTED (HOURS)	MEAN TIME START OF SURGERY (HOURS)	MEAN SURVIVAL (DAYS)	LONGEST SURVIVING ANIMAL IN SERIES (DAYS)
a	No injury, bilateral hip disarticulations	7	Yes	None	–	–	2.8	6.9
b	Bilateral injury, *débridement	12	Yes	None	Immediately	1.9	2.2	6.0
c	No injury bilateral hip disarticulation	5	Yes	Yes	–	–	15.3	32.4
d	Bilateral injury, débridement	15	Yes	Yes	Immediately	2.4	14.7	36.0
e	Bilateral injury, débridement	10	Yes	Yes	6	8.8	4.0	11.2
f	Bilateral injury, débridement	18	Yes	Yes	12	14.5	3.6	12.1
g	Bilateral injury, débridement	5	Yes	Yes	Immediately	24.0	7.7	9.8
h	Bilateral injury, débridement	6	Yes	Yes	Immediately, included local cooling	24.0	14.0 (All but one animal sacrificed at 14 days)	56.0

*Débridement in all instances equivalent to bilateral hip disarticulation.

DISCUSSION

The results of those experiments in which the animals were treated with fluids only corroborate the well-established practice of treating shock from massive wounds with whole blood. Noteworthy, however, is the fact that

transfusion alone did not prevent the death of any animal so treated, even though at least 1,000 c.c. in excess of measured external losses were administered. While the fluid loss into the local wound was not measured, it seems unlikely that this exceeded 1,000 c.c.

The significantly shorter survival times of animals treated with dextran alone cannot be explained with certainty at present. Certainly this observation stands in contrast to the clinically accepted usefulness of this substance as a plasma volume expander.

Treatment with all antibiotics used, with the exception of streptomycin alone, proved highly efficacious in prolonging the survival times of these animals. This efficacy is highlighted by the fact that Chloromycetin, Aureomycin, and penicillin alone and in combination with streptomycin all increased the mean survival time to a greater extent than did treatment with blood alone. In decreasing order of effectiveness in the regimens employed were Aureomycin, chloramphenical, streptomycin in combination with penicillin, and penicillin alone. Procaine penicillin proved more effective than aqueous penicillin as employed in these experiments.

In contrast to the emphasis given by Fine and his groups[9] to the importance of the pretreatment dose in hemorrhagic shock experiments, treatment with penicillin before traumatic shock did not significantly increase the survival of animals compared to those treated only after injury. However, delaying penicillin therapy until 12 hours after injury did not significantly alter the mean survival time from control values.

Orally administered antibiotics were effective in prolonging survival time only when given before injury in sufficient doses to insure a therapeutic blood level of the antimicrobial agent.

Neomycin was ineffective in prolonging survival times even though it was efficacious in reducing the fecal bacterial count.

When oral Aureomycin was delayed until after injury it was ineffective in prolonging survival time. This finding would tend to corroborate the experiences of Altmeier[2] and Cloud[6] who found that orally administered antibiotics were poorly absorbed in the shock state.

Despite the fact that individual animals survive as long as 150 hours with antibiotic treatment, none survived indefinitely. This held true also for the group treated with the combination of fluids and antibiotics. Here the prolongation of survival time in animals treated with penicillin and blood was greater than with each agent alone. The survival of Aureomycin-treated and blood-transfused animals exceeded slightly the survival of animals treated with Aureomycin alone. The use of intravenous dextran apparently vitiated the effectiveness of penicillin therapy. This is in accord with the decreased survival noted above in animals treated with dextran alone. Dextran by hypodermoclysis, however, still allowed some penicillin protection to manifest itself. Saline by hypodermoclysis increased the mean survival of penicillin-treated animals.

The consistency with which survival times were decreased in animals in which intravenous dextran administration was included in the therapeutic regimen deserves special consideration. The intravenous use of dextran was detrimental to the survival of wounded animals in all instances. The effect of dextran in this preparation may be briefly reviewed as follows. (1) The mean survival time of animals treated with dextran was less than the mean survival time of control animals. (2) The mean survival time of animals receiving dextran (1,000 c.c.) plus whole blood equivalent to the total external blood loss was less than animals receiving whole blood only (1,000 c.c. in excess of the total external blood loss). (3) The treatment of animals with intramuscular penicillin dramatically increased the mean survival time when compared to control animals, whereas the mean survival time of animals treated with dextran plus intramuscular penicillin was not significantly different from control values.

The increased survival time of animals treated with intramuscular penicillin and dextran (by hypodermoclysis) is probably entirely due to the beneficial effect of penicillin. Abbott and his associates[1] have demonstrated that dextran administered by hypodermoclysis, with and without hyaluronidase, was recoverable in only very small amounts from the blood stream and that there was no increase in plasma volume, pulse, or blood pressure 4 hours after the administration of 1,000 c.c. of 6 per cent dextran by hypodermoclysis to human beings.

It is only in the last group of experiments, those treated by débridement (bilateral hip disarticulation), that we find permanent recovery from the shock syndrome. With effective fluid replacement, local cooling, and antibiotic therapy, definitive surgery could be delayed for as long as 24 hours with permanent survival. The importance of being able to postpone definitive surgery is obvious in military and mass casualty situations where surgical intervention may not be possible for many hours or days. The beneficial effect of local wound cooling in this preparation cannot be overemphasized. Without local cooling it was necessary to débride within 4 hours of injury to get indefinite survivals.

The results of these experiments focus attention on 2 aspects of the wound shock problem: (1) the role of the local wound in irreversibility and (2) the importance of the bacterial element in the pathogenesis of this syndrome.

Ablation of the hindlimbs of these animals was found to be the only effective form of débridement and the only therapy effective in insuring the survival of these animals. It has been held in many quarters (Blalock, Beard, and Johnson[4]) that the wound served only a passive role in the development of shock in the sense that it constituted a reservoir for the extravasation of blood and plasma. The fact that transfusions did not permanently correct the physiologic derangement and that débridement (that is, amputation) did strongly suggests that some toxic factor was liberated at the site of tissue damage.

The second point of interest is the marked efficacy of the antibiotics. In view of the different structural configuration and mode of action of the various antimicrobial agents used, it seems highly unlikely that their beneficial effect resulted from some nonspecific metabolic effect. In all likelihood their

protective action resulted from direct bacterial suppression. At present the attention of this laboratory is directed toward the elucidation of the exact mechanism and site of this suppressive action as well as the bacterial species involved. From preliminary data it is apparent that the wound is heavily infected with a polymicrobial flora while other tissues remain sterile. It is tempting therefore to suppose that the antibacterial action takes place in the wound or surrounding tissues. It is possible that the toxic substance liberated from the wound as postulated above may be bacterial toxins or consist of some product of bacterial metabolism or some breakdown product of normal tissue liberated as a result of bacterial action.

Recently emphasis has been given to the bacterial element in hemorrhagic shock by Fine and his colleagues.[7] This group, however, has not been able to assign with certainty the site of antibacterial action. Earlier Aub and associates[3, 5, 8, 9] incriminated the *Clostridia* in the pathogenesis of tourniquet shock in dogs. While the role of bacteria in wound shock has not been specifically studied from an experimental point of view, clinical attention has always been given to the aggravating role of infection. It is hoped that this series of studies will serve to delineate the mechanism and importance of the bacterial factor in shock resulting from massive wounds.

CONCLUSIONS

1. A new preparation for the study of shock from massive wounds has been presented.

2. Fluid replacement alone (whole blood) is not sufficient to reverse the shock process in this experimental preparation.

3. All antibiotics used, with the exception of neomycin per os and dihydrostreptomycin by intramuscular injection, are more effective in prolonging the survival time in the wounded animals than is the replacement of blood loss.

4. Lowering of the quantitative fecal bacterial count had no effect on survival time unless the antibiotic was systemically absorbed.

5. Wide spectrum antibiotics prolong survival in the wounded animal more effectively than do those antibiotics in which the antimicrobial activity is more limited.

6. A synergistic survival effect occurs when blood replacement and antibiotics are used in combination as therapeutic agents.

7. In all experiments in which intravenous dextran is used survival times are decreased.

8. Indefinite survivals are realized when blood and antibiotics are administered immediately after wounding and wound débridement is done within 4 to 6 hours.

9. If local wound cooling is added to the above protocol, débridement can be delayed for at least 24 hours with resulting indefinite survivals.

10. From the data it would appear not only that a bacterial factor is involved in some way in the irreversibility of shock in this experimental preparation but also that the primary site of detrimental bacterial activity is the open wound.

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A NEW PREPARATION FOR THE STUDY OF EXPERIMENTAL SHOCK FROM MASSIVE WOUNDS

III. The Effect of Local Wound Treatment on Survival Time

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IN PREVIOUS wound shock experiments[6] it was found that surival times were significantly increased in animals treated with parenterally administered antibiotics and that this prolongation of survival time was greater than that seen when blood replacement was the sole therapy used. When the number of organisms in the gastrointestinal tract was decreased by the oral administrations of antibiotics, the survival time was not increased unless the antibiotic was absorbed into the systemic circulation. On the other hand, débridement of the wound coupled with transfusion and antibiotic therapy resulted in indefinite survivals.

The role of bacterial action in the irreversibility of experimental hemorrhagic shock has been emphasized by Fine and associates.[4] In their hemorrhagic shock preparation, they have not been able to assign, with certainty, the site of detrimental bacterial activity. However, in shock from massive wounds, such as occurs in this experimental preparation, it seemed reasonable to investigate the wound itself as a possible source of bacterial activity which might contribute to the development of the irreversible state. Consequently, a series of survival experiments were carried out in which therapy was confined to the wound. It would seem that this type of study would be especially pertinent to the treatment of mass casualties.

EXPERIMENTAL PROCEDURE

All animals used in these experiments (Texas angora wethers, 4 to 5 years old) were injured by the blast technique as described in a previous publication[8] using the standard tetryl charge (0.494 by 0.795 inches) and M36 detonator cap. The tetryl pellets were placed on a horizontal line one-fourth of the distance from the knee to the greater trochanter of the femur and at the midpoint of the hindquarter muscle mass along that line. Charges were detonated bilaterally in this location. Wound irrigations were carried out using tap water, 0.9 per cent normal sterile saline, 3 per cent hydrogen peroxide, penicillin, Aureomycin, and neomycin. All wound irrigations were begun within one hour

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after injury and were repeated every 2 hours until death of the animal. All damaged muscle was forcefully irrigated so that the therapeutic agent would reach areas well within the confines of damaged muscle. In another group of experiments the wounds were packed with activated zinc peroxide immediately after injury. This procedure was repeated every 6 hours.

In still other experiments in this study, the wounds were treated by the local application of ice to the wounds immediately after injury and this local refrigeration was maintained until the animal's death. In still other experimental groups, local refrigeration was combined with tourniquet application, with systemic antibiotic therapy, and with blood replacement.

All wounds were observed for clinical signs of infection. Since the wounds did not become grossly purulent during the survival span of these animals and since clinical evidence of gas gangrene did not occur, observations denoting clinical infection were limited to the time of appearance of muscle necrosis and odor. Because of obvious difficulties encountered in accurately determining these factors, wound appearance is discussed only in control animals and in those groups in which delay in appearance of these factors was dramatically increased.

RESULTS

Controls.—Although simultaneous controls were run for all experimental groups, statistical comparisons have been carried out using the consolidated group of control animals.

Where comparisons were made between treatment and control groups, a probability value of 0.05 was considered the upper limit of statistical significance.

The mean survival time for the consolidated group of control animals was 19.6 hours (Table I). Only 3 of 117 control animals lived longer than 30 hours.

TABLE I. CONTROL ANIMALS—SURVIVAL TIME IN HOURS

	NUMBER OF ANIMALS	MEAN SURVIVAL TIME (HOURS)	S. E. M.
All control animals	117	19.57	0.53

Within 6 hours after wounding muscle necrosis was apparent in control animals. A definite characteristic odor could be detected in the wounds of control animals within 10 hours after injury.

Irrigation With Tap Water.—The results tabulated in Table II, *A*, indicate that some small amount of protection may be afforded the animal by the simple expedient of wound cleanliness. In this group the mean survival time for those 15 animals irrigated with tap water is 24.1 hours compared to a mean survival of 19.6 hours in the control group of animals in which the only treatment consisted of application of a sterile bandage to the wound. Five hundred cubic centimeters of tap water was used to irrigate each wound every 2 hours.

Samples of venous blood drawn just prior to death in the tap water irrigation group did not show hemolysis in a single instance.

TABLE II. INFLUENCE OF LOCAL WOUND TREATMENT ON SURVIVAL TIME

TREATMENT	NUMBER OF ANIMALS	MEAN SURVIVAL TIME (HOURS)	S. E. M.	P*
A. Irrigation With Inactive Agents				
1. Irrigation with tap water	15	24.1	1.56	.01
2. Irrigation with 0.95 per cent normal saline	15	22.5	2.05	N.S.
B. Irrigation With Oxygen Liberators				
1. Irrigation with 3 per cent hydrogen peroxide	10	21.0	2.2	N.S.
2. Packing with zinc peroxide	10	21.8	1.97	N.S.

*P values compared to consolidated control group of animals.
N.S.—Not significant.

Irrigation With 0.9 Per Cent Normal Sodium Chloride.—The wounds of 15 animals were irrigated with 200 c.c. of 0.9 per cent normal saline on each side every 2 hours.

Again, as in the case of tap water irrigation, there may be a very slight degree of protection afforded these animals when the mean survival times of 22.5 and 19.6 hours are compared in the treatment and control groups, respectively (Table II, *A*).

Wound Treatment With Oxygen Liberators.—It was felt that, since anaerobic bacteria, especially *Clostridium perfringens* can be cultured almost routinely from the wounds and this organism has been incriminated by Aub[1, 2, 5, 7] and others as playing a role in the irreversibility of experimental shock, treatment of the wound with agents which liberate oxygen might prolong survival time by inhibiting growth of these organisms.

The wounds of 10 animals were irrigated with 3 per cent hydrogen peroxide every 2 hours using 200 c.c. of solution in each wound. The mean survival time for the animals thus treated was 21 hours (Table II, *B*). The results suggest that there is little or no protection realized when 3 per cent hydrogen peroxide irrigation is the method of therapy used.

In another group of 10 animals the wounds were packed with activated zinc peroxide every 4 hours. The zinc peroxide was activated before use by heating for 4 hours at 140° F. The results in Table II *B* show that there was no significant increase in survival time by this method of therapy. It should be realized, however, that the zinc peroxide paste could be packed only on the surface of the wound and could not effectively be forced deep into damaged muscle areas as was the case when irrigating solutions were used. (Fig. 1.)

Influence of Application of Ice to Wound.—In Table III, *A*, it will be noted that the mean survival time for 15 animals treated by local refrigeration was 29.0 hours. The efficacy of ice was possibly due to one of 5 mechanisms or a combination of these mechanisms: (1) mechanical cleansing, (2) inhibition of bacterial growth in the wound, (3) delay in muscle proteolysis, (4) a decrease in circulatory exchange at the site of wounding, and (5) a lowered body temperature. The mean rectal temperature of goats in this group prior to treatment with ice was 102.2° F. The mean temperature of these animals prior

to death was 95.0° F. This degree of systemic cooling may in itself have resulted in a prolonged survival time. Future planned experiments, of course, are necessary to prove or disprove this hypothesis.

TABLE III. INFLUENCE OF LOCAL WOUND TREATMENT ON SURVIVAL TIME

TREATMENT	NUMBER OF ANIMALS	MEAN SURVIVAL TIME (HOURS)	S. E. M.	P*
A. Influence of Local Refrigeration Alone and in Combination With Systemic Therapy				
1. Local ice application	15	29.0	3.15	0.01
2. Ice to wound plus tourniquet	10	41.7	7.68	0.01
3. Ice to wound plus blood transfusions	10	34.7	2.34	0.01
4. Ice to wound plus intramuscular penicillin	14	61.9	7.16	0.01
B. Irrigation With Antibiotics				
1. Irrigation with neomycin	8	19.2	2.16	N.S.
2. Irrigation with penicillin	11	45.4	9.53	0.01
3. Irrigation with Aureomycin	11	48.4	14.9	0.02

*P values compared to consolidated control group of animals.
N.S.—not Significant.

The wounds of animals treated with ice were especially striking. Even at death, gross muscle necrosis was not observed. The characteristic pungent odor which was typical of the wounds of control animals did not develop in the experimental groups treated with ice.

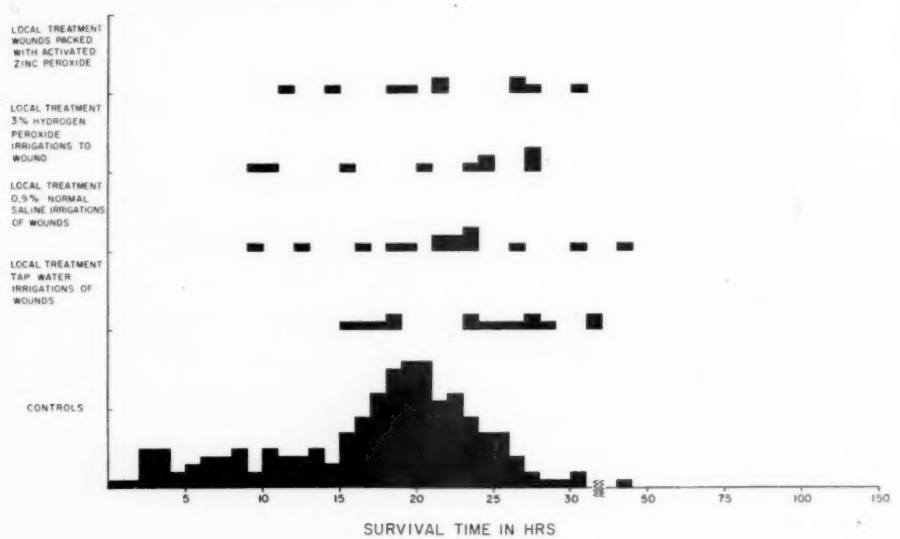

Fig. 1.—Wound irrigation with tap water, saline, and oxygen liberators. Each small bar represents a single animal.

In animals treated with ice applications to the wound, the range of survival varied from 8 to 43 hours with 9 of 15 animals living beyond 30 hours. In the control group, only 3 of 117 animals lived beyond 30 hours (Table IV.)

Irrigation With Antibiotics.—Irrigation with antibiotics was done because it was felt that a major site of bacterial activity affecting the clinical course of the wound shock was the wound itself. There may well be, and probably are, other areas where bacterial activity plays a part in the productions of

TABLE IV. PERCENTAGE OF ANIMALS LIVING BEYOND 30 HOURS

EXPERIMENTAL GROUP	TOTAL NUMBER OF ANIMALS	NUMBER LIVING BEYOND 30 HOURS	PER CENT OF ANIAMLS LIVING BEYOND 30 HOURS
A. Control group	117	3	2.6
B. Irrigation with inactive agents			
1. Irrigation with tap water	15	2	13.3
2. Irrigation with 0.9 per cent normal saline	15	2	13.3
C. Irrigation with oxygen liberators			
1. Irrigation with 3 per cent hydrogen peroxide	10	0	0.0
2. Packing with activated zinc peroxide	10	1	10.0
D. Local ice to wound alone and in combination			
1. Local ice application	15	9	60.0
2. Local ice application and tourniquets	10	7	70.0
3. Local ice application and blood	10	8	80.0
4. Local ice application and intramuscular penicillin	15	13	86.7
E. Irrigation with antibiotics			
1. Irrigation with neomycin	8	0	0.0
2. Irrigation with penicillin	11	7	63.6
3. Irrigation with Aureomycin	11	8	72.7

irreversible shock in the injured animal. The intestinal tract, for example, may be another area where detrimental bacterial activity occurs, as Dr. Fine and co-workers[3] suggest from work on their hemorrhagic shock preparation. However, since intestinal sterilization in a few experiments did not effectively increase survival times in this preparation and since systemic antibiotics effectively prolonged survival times, it seemed logical that the wound was a primary source of detrimental bacterial activity. Other factors in previous studies added impetus to this suspicion. Tourniquet application to the wound, for example, increased survival times slightly.* Indefinite survivals were obtained where systemic penicillin and blood replacement therapy were combined with adequate aseptic surgical débridement of the wounds.[6]

In these experimental groups 3 antibiotics were used; namely, crystalline potassium penicillin, Aureomycin hydrochloride, and Mycifridin (a brand of neomycin sulphate). Concentrations of solutions were as follows: (1) for penicillin, 5,000 units per cubic centimeter, (2) for Aureomycin hydrochloride, 2.5 mg. per cubic centimeter, and (3) for Mycifridin sulphate, 2.5 mg. per cubic centimeter. Initial irrigations of 200 c.c. to each wound were followed at 2-hour intervals by 100 c.c. irrigation of each wound with the above solutions. The results of these studies can be seen in Table III, *B*. Irrigation with penicillin effectively prolonged survival time to a mean of 45.4 hours in 11 animals. The survival spread in this group was from 9.7 hours to 118.5 hours with most animals living approximately 50 hours. Seven of 11 animals in this group lived longer than 30 hours.

Much the same results were seen when Aureomycin hydrochloride was used as the irrigating solution. The mean survival time for this group of 11 animals was 48.4 hours. The range of survivals in this group varied from 9.3 to 184.4 hours. Eight of 11 animals in this group lived beyond 30 hours.

*Mean survival time for 10 animals when tourniquets were applied to upper part of wound was 26 hours.

Irrigation with neomycin solution in 8 animals did not effectively increase survival time as is shown in Table III, *B*. The reason for this is not entirely clear. On the contrary, neomycin, which is extremely effective against the intestinal flora might logically be expected to effectively prolong survival since the wound contaminants in this preparation are for the most part organisms of the intestinal flora group. One possible explanation is that absorption of the drug through damaged muscle areas into the systemic circulation counteracted any local beneficial effects by virtue of the nephrotoxic and neurotoxic properties of the drug. It is also possible that depression of the other fecal flora allowed uninhibited growth of certain anaerobes especially *Clostridium perfringens*. (Fig. 2.)

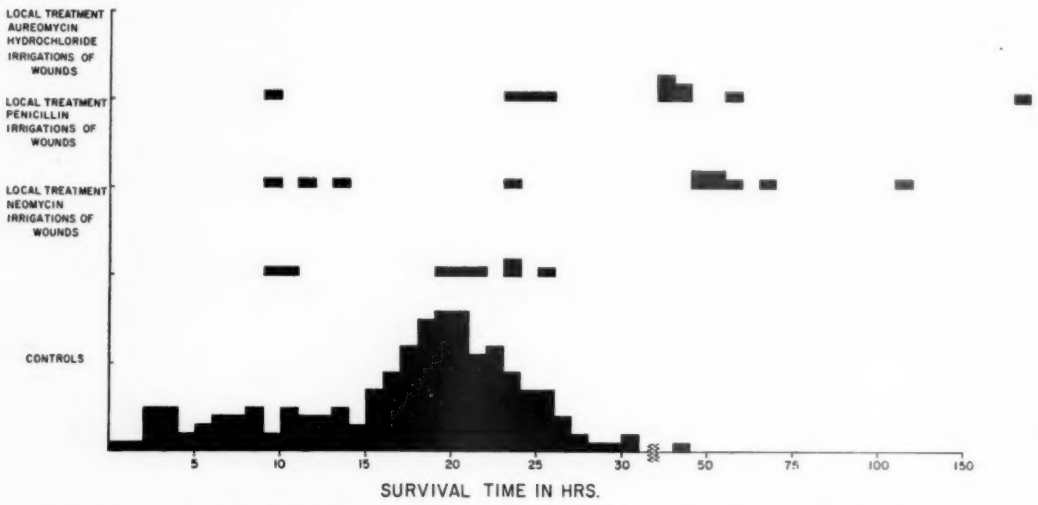

Fig. 2.—Wound irrigation with antibiotics. Each small bar represents a single animal.

In comparing the survival times of animals treated by penicillin and Aureomycin irrigation, one might expect Aureomycin to be superior because of its wide spectral range of antibiotic activity. The longest living animal (184.4 hours) was in the Aureomycin group. However, the sclerosing properties of Aureomycin are well known, and the forceful irrigation of this solution into muscle tissue may cause irreversible damage to muscle which might otherwise maintain viability. This, however, was a clinical impression gained from treatment of these groups and not backed up by microscopic studies. Statistical comparison of the 2 groups reveals no significant difference in survival times.

In the wounds of animals irrigated with antibiotics, we were not able to observe any striking delay in the appearance time of muscle necrosis. However, there was a definite delay in the appearance time of the characteristic pungent odor to 26 ± 6 hours.

Since local refrigeration of the wound seemed to give such promising results, it was decided to combine this mode of therapy with other forms of treatment previously reported.[6]

Local Refrigeration and Tourniquet Application.—In using tourniquet applications, it was virtually impossible to completely isolate the wound because

of its extent. However, it is estimated that there was at least 75 per cent isolation of the wound using the tourniquet technique. When tourniquet application and local refrigeration were combined as a means of therapy, the mean survival time was 41.7 hours as compared to 19.6 hours for the control group. In a previous study where tourniquets alone were used, the mean survival time was 26 hours as compared to 18.9 hours for the control group. It would appear that in the light of the bacterial factor theory of shock that the efficacy of the combination of these methods of treatment may be due to a more effective blockage of absorption of bacterial toxins or metabolic products of bacterial activity from the wound plus an inhibition of bacterial growth and possibly toxin production.

Penicillin and Local Refrigeration.—If systemic penicillin therapy (600,000 units immediately postblast and 300,000 units every 6 hours) is combined with local refrigeration, the mean survival time is increased to 61.9 hours. This may be again compared to penicillin-treated animals reported previously when systemic intramuscular therapy was withheld until the immediate postinjury period. The mean survival time in the latter group was 54 hours. (Fig. 3.)

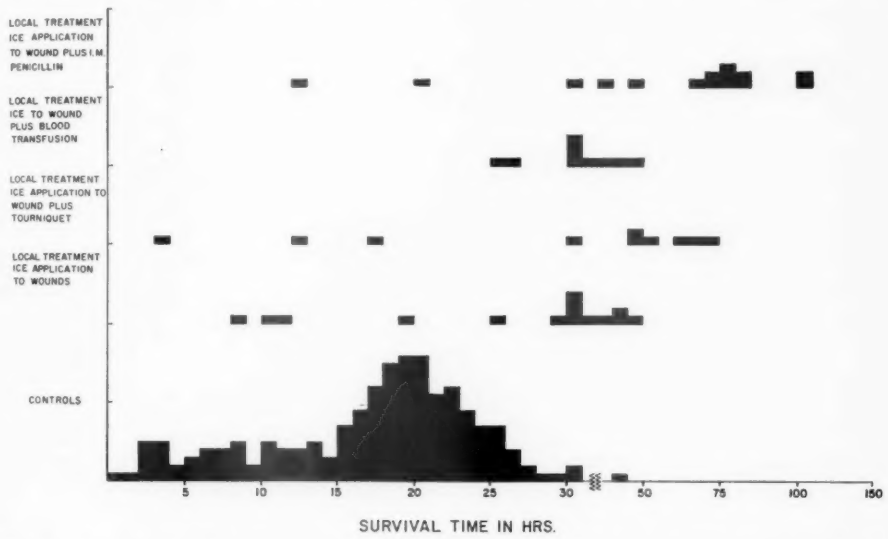

Fig. 3.—Ice application to wounds alone and in combination with other local and systemic methods of therapy. Each small bar represents a single animal.

DISCUSSION

The foregoing statistical data add more evidence that a bacterial factor is at least partly responsible for the irreversibility of wound shock. Since in other experiments it was demonstrated by blood cultures that septicemia per se was not a factor in the lethality of this preparation, it is reasonable to assume that the bacterial factor may be, in reality, bacterial toxins or other products arising secondary to bacterial metabolism in the wound. Furthermore, it would seem that in shock from massive wounds, a logical site of detrimental bacterial activity is the wound itself. This is given additional weight by the facts that any treatment directed toward the isolation of the wound and its blood supply

and venous return or treatments which inhibit bacterial growth in the wound result in effective prolongation of survival time. In previous studies,[6] surgical débridement of the wound coupled with transfusion and antibiotic therapy resulted in complete reversal of the shock process.

The deaths in animals dying in the first 10 hours of the postinjury period are difficult to explain. It may well be that animals dying early in the post-blast period die primarily of hemorrhage, although it is not definitely established that bacterial factors do not play a role in the death of the animal even at that early date. It would seem that this depended somewhat upon the wound inoculum and the circulatory exchange present in the area of damaged muscle which, of course, must vary somewhat with each animal. Dr. Fine and associates[9] have demonstrated in their hemorrhagic shock preparation that the hypovolemic animal is much more susceptible to the action of bacterial toxin than is the normovolemic animal. Death due to hemorrhagic shock in the group of early-dying animals has not been proved. Indeed, statistical analysis shows no correlation between either initial or total external blood loss and survival time.[8]

It is difficult at best to interpret any experimental finding on animals in the light of therapy of human beings. We do not suggest that these local forms of treatment be used solely for the treatment of wound shock, especially when adequate blood and blood substitutes are available. Everyone recognizes that there is no substitute for blood loss as effective as whole blood replacement. However, in the event of large numbers of casualties, blood and effective means of surgery will not be available to everyone, and it is the purpose of this group of studies not only to add some knowledge regarding the etiology of wound shock but also to suggest possible effective means of prolonging life, if and when the combination of large numbers of casualties and lack of immediately available hospital facilities and surgical skills constitute a reality. With this in mind, the following possible treatments are suggested.

1. If it is obvious in an extremity wound that amputation is inevitable, these experimental findings suggest that the application of a tourniquet to the wound and the application of ice, or other forms of local cooling, if available, to the extremity may be an effective means of prolonging life. When possible, this should be done in combinations with systemic antibiotic therapy.

2. If the wound is in an area where application of a tourniquet is not feasible or if the wound is an extremity wound in which blood loss has been controlled and a viable limb is expected as an end result, the use of systemic antibiotics plus local cooling of the wound may be efficacious. It is cautioned, however, that the application of ice should be tempered at all times by sound clinical judgment so that irreversible changes do not occur in the vascular tree.

3. If antibiotics alone are available, previous work has shown that systemic antibiotic therapy is effective in prolonging survival. It is reasonable to assume that systemic therapy may be even more efficacious if combined with antibiotic wound irrigations. Further study is necessary to indicate final antibiotic superiority. In the light of these experimental findings, it may seem that Aureomycin may be most effective. However, its local use as an irrigating agent cannot be fully recommended at present until its effect on muscle tissue and the vascular tree within the wound is further clarified.

4. If no other means of therapy are available, there is some experimental evidence that the simple expedient of cleansing the wound may be effective in prolonging life in wound shock.

The mere surface washing or surface irrigation of the wound does not effectively prolong survival. The fact that all of these irrigations were forceful into areas of damaged muscle is probably an important factor in prolonging survival. The moderately anoxic areas of damaged muscle within the wound are excellent areas for bacterial growth. Forceful irrigation of these damaged muscles directs therapy to these vital areas.

CONCLUSIONS

1. Experimental findings of local therapy in wound shock have been presented.

2. The possible application of these methods of treatment to large numbers of casualties is discussed.

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A NEW PREPARATION FOR THE STUDY OF EXPERIMENTAL SHOCK FROM MASSIVE WOUNDS

IV. The Effect of Penicillin and Streptomycin on the Quantitative Bacteriologic Flora of the Wound

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PREVIOUS work in this series[7] has highlighted the dramatic effectiveness of certain antibiotics in the prolongation of survival of goats dying of massive wounds. It will be remembered that the administration of penicillin in an optimal regimen increased the average survival of animals from a control value of 20 hours to 55 hours, whereas effective whole blood replacement increased the mean survival only to 36 hours. Those antibiotics found effective in prolonging the life of injured animals were penicillin, chlortetracycline, and chloramphenicol. Those found ineffective were oral neomycin and systemic dihydrostreptomycin in the regimens employed. All animals, regardless of systemic therapy, eventually died as a result of the injury sustained. However, when effective débridement was carried out in the form of bilateral amputation at the hips,[7] the animals completely recovered from the initial injury. This disclosure, along with consideration of the relative refractoriness of the wounded goats to blood transfusions, led us to postulate the elaboration of some toxic factor from the wound site.

These survival studies suggested to us that bacteria proliferating in the wound might yield the postulated toxic factor, either by the elaboration of classical toxins or by the breakdown of normal tissue constituents. The failure of virtual bowel sterilization with oral neomycin to increase survival was taken as evidence against the possibility that the antibiotics exerted their action by depressing the intestinal bacterial flora. Intensive blood cultures of the untreated animals failed to reveal any consistent bacteremia.[1] However, the possibility of an agonal bacteremia in the dying animal is now being investigated at these laboratories.

Because of the strong likelihood that bacterial activity in the wound might play an important role in the early death of the wounded animals, our attention was focused on the bacteriology of the wound. Work of others with this

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preparation[1] had demonstrated that the bacterial population was a polymicrobial flora, with representatives of the gram-negative coliform organisms, the gram-positive cocci, and aerobic and anaerobic gram-positive spore formers being present almost invariably in all cultures. It was also noted that treatment with penicillin and other antibiotics failed to alter the qualitative flora. This observation was validated in our own hands in a small series of animals (Table I).

TABLE I. WOUND CULTURES

HOUR AFTER INJURY	0		6		12		18		48
TREATMENT	C	P	C	P	C	P	C	P	P
Organisms found									
Micrococcus sp.	2/2*	3/3	2/2	3/3	2/2	3/3	4/4	3/3	3/3
Streptococcus sp.	2/2	2/3	2/2	3/3	2/2	3/3	3/4	3/3	3/3
Bacillus sp.	2/2	3/3	2/2	3/3	2/2	3/3	3/4	3/3	3/3
Clostridium sp.	1/2	2/3	1/2	3/3	1/2	3/3	4/4	3/3	3/3
Escherichia coli	2/2	2/3	1/2	3/3	2/2	3/3	3/4	3/3	3/3
Aerobacter aerogenes	0/2	3/3	2/2	2/3	2/2	3/3	3/4	2/3	0/3
Paracolon type org.	2/2	3/3	2/2	3/3	2/2	3/3	2/4	3/3	3/3
Salmonella sp.	0/2	0/3	0/2	0/3	1/2	1/3	1/4	1/3	0/3
Proteus sp.	0/2	0/3	0/2	0/3	0/2	0/3	2/4	1/3	3/3
Pseudomonas sp.	0/2	0/3	0/2	0/3	0/2	0/3	2/4	0/3	0/3
Neisseria catarrhalis	0/2	1/3	0/2	0/3	0/2	0/3	0/4	0/3	0/3

C—Control animals.
P—Penicillin-treated animals.
*Ratios expressed as number of animals positive for organism to total number of animals examined.

Failure to demonstrate changes in the qualitative bacterial flora with antibiotic treatment led us to turn our attention to the quantitative aspects of the problem. It was our hope to make a correlation between the effects of penicillin therapy and the quantitative bacteriologic status of the wound. Streptomycin was also chosen for evaluation because of (a) its strikingly different antibacterial spectrum and (b) the ineffectiveness of dihydrostreptomycin in prolonging the survival of the animals. It was hoped that consideration of the data gathered from both penicillin and streptomycin studies might allow us to make a reasonable guess as to the general classification of the offending organisms.

MATERIALS AND METHODS

Wounding.—The animal preparation has been more extensively described in a previous communication.[8] Texas Angora wether (castrated) goats were wounded by bilateral detonation of tetryl (a high explosive) charges on predetermined areas of the thighs. Extensive soft tissue wounds, accompanied invariably by compound fractures of the femurs, were thus created. Hemostasis was effected within minutes of the blast by clamping the major bleeding vessels. The external blood loss varied between 100 and 400 c.c. The wounds were packed with gauze and a stockinette was applied to both hindlimbs. A plastic bag was applied near the anus to prevent gross fecal contamination. However, no attempt at sterile technique either in the preparation or the handling of the animals was made. Bacterial contamination was considered to arise from the surrounding air, the skin and hair of the animal, and the hands of the

operators. Contamination was thought to arise entirely from exogenous sources since the normal muscle of the goat, unlike that of the dog, is entirely sterile.[1]

Antibiotic Administration.—Penicillin was given in the following regimen: 300,000 units of procaine penicillin and 1,000,000 units of aqueous crystalline penicillin intramuscularly one hour prior to injury, the same combination immediately after injury, and every 8 hours thereafter. In the streptomycin series, one gram of streptomycin intramuscularly was given one hour prior to wounding, 0.5 Gm. shortly after injury, and 0.5 Gm. every 8 hours thereafter.

Determinations of penicillin-treated animals were interspersed with determinations of control animals so as to assure maximal uniformity in these series. The streptomycin animals, however, were sampled in one 2-week period, after the completion of the rest of the experiment.

Wound Sampling.—Muscle samples weighing between 5 and 10 Gm. were obtained from the lacerated edge of the left quadriceps femoris group. A number of considerations led us to choose this muscle for wound sampling. In the first place, it was easily identifiable in all injured animals. Almost always the muscle was extensively lacerated, roughly at right angles to the direction of its fibers. When biopsied, it invariably bled. This was interpreted to signify that active metabolic exchange could take place, with absorption of possible toxic factors and delivery of antibacterial substances from the systemic circulation.

Biopsies were taken immediately after injury (0 hours) and 6, 12, and 18 hours after wounding in control, penicillin, and streptomycin-treated animals. An additional sample was obtained at 48 hours in penicillin-treated animals. The zero hour sample was obtained within minutes after the explosion and was plated within 20 minutes after injury. Only one sample was obtained from each animal employed in order to avoid the possible deleterious influences of repeated biopsies, such as bleeding, and the introduction of new infection.

Processing of Biopsy Material.—The muscle samples biopsied were carefully weighed under sterile conditions. The muscle was then churned in a metal Waring blender with the addition of 10 c.c. of sterile water per gram of tissue. Serial tenfold dilutions were prepared. One cubic centimeter of each dilution prepared was pipetted into pour plates. In general, only one plate was prepared for each dilution. A gram stain was prepared of a direct smear of the original homogenate.

Media.—Three bacteriologic media were employed, nutrient, azide, and endo agar. Nutrient agar (Difco) was used to support the growth of both gram-positive and gram-negative aerobic organisms, whereas the azide agar (Difco nutrient agar + 0.07 per cent NA azide) was employed to inhibit gram-negative bacteria,[10] and endo agar (Difco) to inhibit gram-positives.[3] In order to check the differential selective power of endo and azide agars, colonies from pour plates were picked and gram-stained. In 3 separate experiments it was determined that roughly 50 per cent of gram-negative and gram-positive colonies were suppressed by azide and endo agars, respectively. In the initial phase of these studies only nutrient agar was used. In the later stages, the

3 media were used simultaneously. For this reason, a larger number of nutrient agar determinations are recorded in the results of the quantitative studies.

Incubation and Counting.—Plates were incubated for 48 hours at 37° C. under aerobic conditions, at the end of which time they were counted with the aid of a Quebec Colony Counter. In general only plates bearing between 30 and 300 colonies were used for calculations of the bacterial concentration. However, when the lowest dilution had less than 30 colonies it was nevertheless used to estimate the bacterial count.

Bacteriologic Wound Topography.—In order to assay the spatial extent of wound infection 18 hours after injury, small sterile scalpel incisions were placed in a grid-like fashion over the lateral plane of the quadriceps muscle group. Sterile cotton swabs were introduced into these incisions and twisted throughout the depth of the muscle. The swabs were then thoroughly stirred in a test tube containing 10 c.c. of sterile water, and serial dilutions of this tube were prepared. The original tube and subsequent dilutions were then plated and incubated for 48 hours. From 16 to 24 points were thus evaluated in each muscle studied. Altogether 4 control animals were thus studied; in 2 the quadriceps was removed surgically before study and in 2 the muscle was studied in vivo while the animal was under Nembutal anesthesia. Three penicillin-treated animals were studied, 2 in vivo and one in vitro.

Histologic Sections.—Eighteen hours after injury various areas of the quadriceps groups were sectioned, starting from the relative necrotic muscle at the lacerated edge and progressing inward to the more viable regions. Tissues were fixed in 10 per cent Formalin and stained with hematoxylin and eosin as well as Brown and Brenn stain[2] for bacteria.

RESULTS

Effect of Penicillin.—Table II summarizes the quantitative bacteriologic data in control and experimental groups. The bacterial count is expressed in terms of the logarithm to the base 10 of the number of bacteria per gram of tissue. Thereupon all statistical operations are performed on the basis of the logarithmic function. It should be noted that the assessment of statistical significance of difference between experimental and control groups at a particular hour takes into consideration only values determined at that hour and disregards the influence of determinations at other time intervals. The data comparing the control and penicillin groups is graphically represented in Fig. 1.

By inspection of the graph it can be seen that the bacterial counts of control wounds rose in a roughly exponential fashion until 12 hours when a slight decrease in rate of increase was noted. It can also be seen that the most prominent effect of penicillin was the suppression of bacterial growth for the first 6 hours of the experiments. Thereafter, the bacterial count rose rapidly, so that at 18 hours there was no significant difference between control and penicillin-treated wounds. It also appears that the azide medium

TABLE II. STATISTICAL EVALUATION OF BACTERIAL COUNTS FROM THE QUADRICEPS FEMORIS

HOUR	0			6			12			18			48		
MEDIUM	A	E	NA	A	E	NA	A	E	NA	A	E	NA	A	E	NA
Control															
m_c	1.63	0.97	2.05	3.67	3.33	3.55	5.42	5.21	5.71	5.89	5.79	6.18			
n	11	11	17	9	9	15	10	10	15	12	11	20			
SD	0.37	0.81	0.65	1.11	1.11	1.14	0.70	0.98	0.81	0.97	1.02	0.78			
SEM	0.11	0.24	0.16	0.37	0.37	0.29	0.22	0.31	0.21	0.28	0.31	0.17			
Penicillin															
m	1.82	1.55	2.11	1.56	1.97	2.35	4.50	4.66	5.30	5.68	5.76	6.17	5.89	6.58	6.71
n	10	10	11	8	8	10	12	11	13	10	10	12	9	9	11
SD	0.83	1.16	1.02	0.79	0.75	0.83	1.08	0.99	0.91	1.31	1.05	0.99	1.43	0.72	0.64
SEM	0.26	0.37	0.31	0.28	0.23	0.26	0.31	0.30	0.25	0.42	0.32	0.30	0.48	0.24	0.19
$m - m_c$	+0.19	+0.58	+0.06	−2.11	−1.36	−1.20	−0.92	−0.55	−0.41	−0.21	−0.03	−0.01			
t	0.669	1.318	0.172	4.557	3.097	3.045	2.395	1.273	1.253	0.417	0.067	0.029			
p	>0.5	>0.1	>0.5	<0.01	<0.01	<0.01	<0.05	>0.2	>0.2	>0.5	>0.5	>0.5			
Streptomycin															
m	1.31	0.72	1.66	3.24	2.70	3.04	5.56	4.95	5.56	5.51	4.63	5.60			
n	10	10	10	9	9	8	10	10	10	10	10	10			
SD	0.75	0.64	0.64	1.08	1.08	0.89	1.00	0.87	1.00	0.87	1.51	0.83			
SEM	0.24	0.20	0.20	0.36	0.36	0.31	0.32	0.28	0.32	0.27	0.48	0.26			
$m - m_c$	−0.32	−0.25	−0.45	−0.43	−0.63	−0.51	+0.14	−0.26	−0.15	−0.38	−1.16	−0.58			
t	1.221	0.788	1.750	0.833	1.218	1.186	0.361	0.622	0.396	0.969	2.045	1.835			
p	>0.2	>0.4	>0.05	>0.4	>0.2	>0.2	>0.5	>0.5	>0.5	>0.3	>0.05	>0.05			

A—Azide agar.
E—Endo agar.
NA—Nutrient agar.

m—Mean (experimental) $\log_{10}$ number bacteria per gram muscle.
m_c—Mean (control) $\log_{10}$ number bacteria per gram muscle.
n—Number of determinations.
SD—Standard deviation (±).
SEM—Standard error of mean (±).

$m - m_c$ = difference of means.

$$t = \frac{m - m_c}{\sqrt{SEM_c^2 + SEM^2}}.$$

p = probability that $m - m_c = 0$.

was the most sensitive parameter of penicillin action, even though the suppressive action of penicillin in the first 6 hours was reflected to a somewhat lesser extent in the other media.

Since the depression of bacterial concentration appeared limited to the first 18 hours, it was thought to be of interest to determine whether or not penicillin had any effect in decreasing the *extent* of infection at 18 hours.

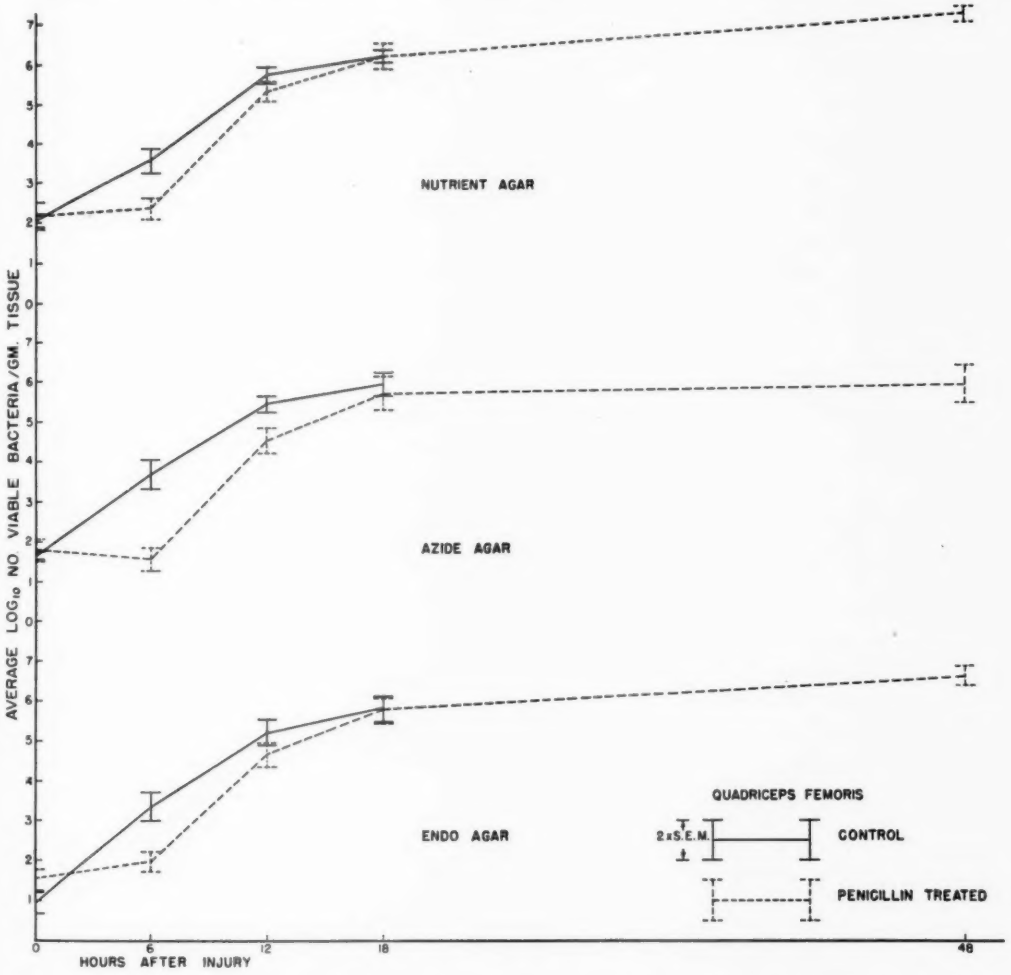

Fig. 1.—Effect of penicillin on the bacterial concentration at the damaged end of the quadriceps femoris.

This was accomplished by mapping the spread of infection in the quadriceps, as outlined in the previous section. The results of all experiments indicated that the infection appeared limited to a depth of from 2 to 3 cm. from the lacerated edge of the muscle. There was no evidence from gross inspection of the results that penicillin had any effect whatsoever on the volume of infected muscle. These observations, as all others in this report, are confined to aerobic and facultative anaerobic organisms only.

Histologic studies confirmed the topographic experiments in indicating that the bulk of infection was limited to a depth of about 2 cm. from the

lacerated edge of the muscle, even though structural degenerative changes occurred several centimeters further in.

Effect of Streptomycin.—The results of quantitative studies are summarized in Table II, while they are graphically represented in Fig. 2.

There is some suggestion that a depression of bacterial count became manifest at about 12 hours after injury. This effect was most prominent in the endo agar determinations.

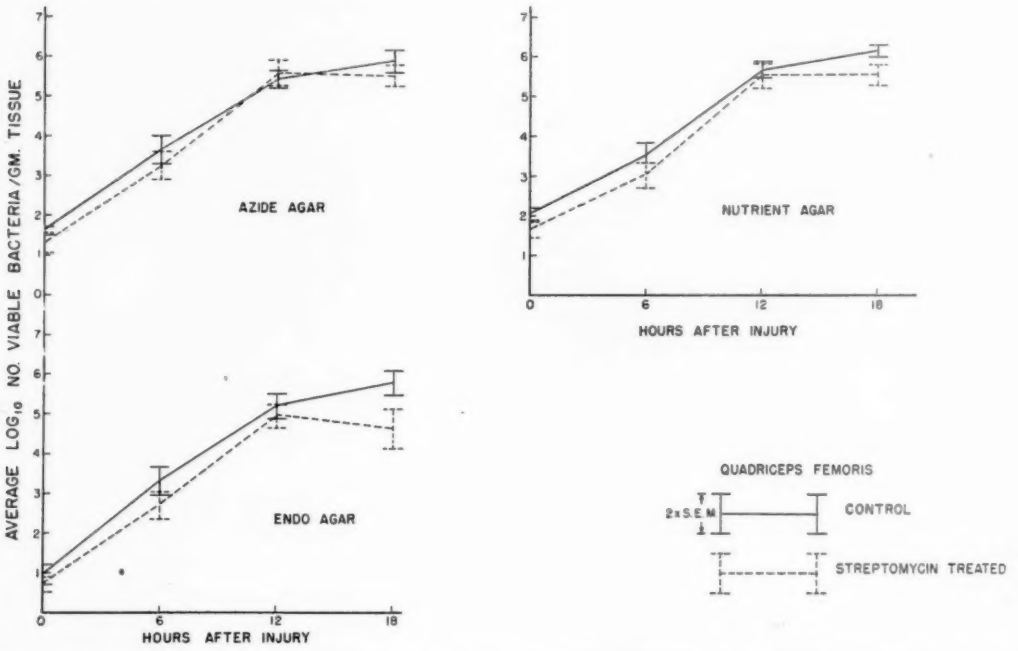

Fig. 2.—Effect of streptomycin on the bacterial concentration at the damaged end of the quadriceps femoris.

DISCUSSION

It must be emphasized at the outset that the use of differential media did not represent an effort to segregate the bacterial populations into 2 distinct classes, the gram-positive and the gram-negative organisms. This was certainly not possible owing to the large degree of overlapping that occurred with azide and endo agars as used in our hands. These media were simply introduced to find more sensitive parameters of penicillin and streptomycin action.

It should also be noted that the number of bacteria is expressed as the average of the logarithms of the number of bacteria per gram of tissue. This mathematical representation is most desirable because the logarithms of the bacterial concentration distribute themselves normally, while the numbers themselves do not. Thus, if one were to use the arithmetic mean of the number, this figure would be weighed in favor of a few high determinations.

The results indicate that the most pronounced effect, in terms of difference in logarithms, occurred within the first 6 hours after injury. The depression

of count was most prominent with the use of azide agar, even though the effect was manifest in the other media employed. A possible explanation of these facts is that penicillin acts primarily on the gram-positive bacteria and that the depression in the endo agar simply reflects the large overlaps of bacterial population found in these differential media. On the other hand, it is not possible to rule out a secondary effect by penicillin on the gram-negative bacteria, either by a direct action or indirectly through depression of gram-positive organisms.

After the initial depression, the bacterial counts in penicillin-treated animals rose rapidly, so that at 18 hours no difference existed between them and control values. At the same time at 18 hours no difference in the spatial extent of bacterial infection existed between control and penicillin-treated animals, as judged by the topography experiments. Also, as mentioned in the introduction, there was no apparent difference in the general nature of the bacteria in the 2 groups. These facts are also substantiated by the observation that at 18 hours there was no striking difference in the gross appearance in the wounds of treated and untreated animals.

Because of the large spread of individual values it is difficult to come to any firm conclusion regarding the effect of streptomycin on the bacterial wound population. There is a suggestion, however, that streptomycin did cause a suppression of bacterial growth of gram-negative organisms between 12 and 18 hours. The impression was re-enforced by the observation that direct smears of the homogenates of biopsy specimens of streptomycin-treated animals at 18 hours appeared to show a much larger percentage of gram-positive organisms than control preparations.

It is difficult to determine with certainty how far these results explain the beneficial action of penicillin in prolonging the survival of wounded animals. If one chooses to attribute the protection afforded by penicillin to the observed reduction in the bacterial flora, one must attempt to explain why this antibiotic increases the mean survival of the animal to 55 hours while reducing the bacterial count for only 18. A working hypothesis to explain this apparent paradox can be suggested. The wounded animal immediately after injury and hemorrhage loses its normal defenses against products of bacterial metabolism. It becomes exquisitely sensitive even to small quantities of some toxic factor elaborated by the bacteria. Penicillin is effective by an initial suppression of bacterial proliferation, thus allowing the animal to regain its normal resistance to the hypothetical factor. Once resistance has been regained, say by the eighteenth hour, the animal could then continue to survive for additional hours without the benefit of the antibiotic. The final cause of death could then represent either the effect of cumulative infection or some other unrelated factor.

This hypothesis is in accord with some other known facts about this preparation. If only one dose of penicillin is administered to the animal shortly before or shortly after injury, the animal will have a significant increase in survival time (37 hours). If, however, treatment is delayed for 12 hours,

no significant increase in survival is noted. These facts stress the importance of early antibacterial treatment in this preparation. Furthermore, the work of Dr. Fine's group[5] has shown increased sensitivity of animals in hemorrhagic shock to bacteria and products of bacterial metabolism.

Other explanations of the effect of penicillin, however, remain to be considered. It is possible that while no single bacterial species is entirely eliminated, a group of bacteria such as the *Clostridia* could be quantitatively suppressed without altering the parameters employed in these experiments. An evaluation of the role of anaerobes is now being carried out in our laboratory. The *Clostridia* deserve special emphasis in view of the work of Pope and associates[9] who incriminated these species in the pathogenesis of tourniquet shock in rats.

The data gathered in these experiments taken in conjunction with the survival studies make it likely, though far from certain, that the primary offending bacteria are of the gram-positive penicillin-sensitive variety. The failure of streptomycin to prolong the survival time could be interpreted on the basis of its primarily gram-negative antibacterial range; alternatively, one could ascribe the therapeutic failure to the fact that streptomycin appears to act later than penicillin in suppressing bacterial growth.

It may be of interest to compare the results of these studies to those of Fine's group, who have demonstrated a significant protection by antibiotics of dogs subjected to hemorrhagic shock.[5] The necessity for early antibacterial treatment parallels our findings.[6] However, among the effective antibiotics these workers include oral neomycin, which was not effective in our preparation. Furthermore, the origin and nature of the bacteria operative in hemorrhagic shock have not been defined.

SUMMARY

1. Curves have been established describing the growth of bacterial populations in a representative muscle of a massive experimental wound.

2. The effect of penicillin and streptomycin on the growth pattern of bacteria in wounds has been studied, employing nutrient, azide, and endo agars as differential media. The wounds of penicillin-treated animals showed a marked initial depression in bacterial counts lasting 6 hours. Thereafter the count rose rapidly, approximating control levels at 18 hours. Azide agar, which inhibits the growth of gram-negative bacteria, was the most sensitive parameter of penicillin action.

3. At 18 hours after injury, the total spatial extent of infection did not seem to differ in penicillin and untreated animals.

4. There was some suggestion that streptomycin suppressed bacterial proliferation beginning 12 hours after injury. This effect appeared to be most marked with endo agar, which was employed to inhibit gram-positive bacteria.

5. The relation of these findings to the increased survival afforded by certain antibiotics was discussed.

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A NEW PREPARATION FOR THE STUDY OF EXPERIMENTAL SHOCK FROM MASSIVE WOUNDS

V. Changes in Some Serum Electrolytes and Nitrogenous Fraction Values

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THE investigations reported in this paper describe alterations in the concentrations of various blood serum constituents (electrolytes and certain nitrogen-containing components) in animals subjected to massive lethal soft tissue damage. In addition, a comparison is made between the sera of untreated and penicillin-treated animals which sustained similar wounds. The third group of studies was made on the sera of uninjured animals in which lethal shock was induced by the intravenous injection of endotoxin prepared from a pure culture of *Escherichia coli.*

EXPERIMENTAL PROCEDURE

Texas Angora goats weighing 36 to 50 Kg. were used in these investigations. The animals were wounded by a technique previously reported by Oschsner and associates.[6]

Two groups of wounded animals studied were (1) control animals which had no treatment other than hemostasis and sterile dressings and (2) animals receiving 1,000,000 units of aqueous penicillin and 300,000 units of penicillin in oil before wounding and every 8 hours subsequently until the death of the animal. An additional group of unwounded animals received a lethal intravenous injection of gram-negative endotoxin. The endotoxin administered was prepared from a pure culture of *Escherichia coli* taken from a goat's wound. Identical assays were carried out on the blood of all animals.

A 30 c.c. sample of heparinized blood was taken from each animal before wounding or injection with toxin. Subsequent samples were taken at 6, 14, 18, and every 24 hours thereafter until the death of the animals. A preterminal blood sample was obtained just prior to death.

The blood plasma components assayed may be divided into 2 groups, electrolytes and nitrogen-containing constituents. The electrolytes measured were potassium, sodium, magnesium, calcium, and inorganic phosphate. The nitrogen-containing group includes nonprotein nitrogen, blood urea nitrogen, creatine, creatinine, and amino acid nitrogen.

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The plasma sodium and potassium levels were determined by the use of a Beckman flame photometer. The inorganic phosphate was assayed by the Shinowara technique[7] and magnesium and calcium by the chelation method as modified by Dziemian and Ingram.[1] The nonprotein nitrogen studies were done by the Folin and Wu method,[3] blood urea nitrogen by the urease method of Folin and Svedberg,[2] creatine and creatinine by the Folin and Wu technique,[3] and amino acid nitrogen according to Frame, Russell, and Wilhelmi.[4] All the latter determinations are photometric and a Coleman Jr. spectrophotometer was used during the course of the investigation.

RESULTS

Plasma Sodium.—No significant changes in the plasma sodium concentrations were encountered in animals from any of the groups (Tables I, II, and III). Average values remained quite constant regardless of the length of survival of the animals. A slight fall in the initial determinations after wounding is accounted for by the variable loss of blood at the time of wounding.

Plasma Potassium.—The determination of potassium was found to be complicated by the excessive fragility of the goat erythrocyte. Just the small amount of manipulation involved in this procedure caused some hemolysis and, since the goat erythrocyte does contain significant amounts of potassium, large fluctuations in the values we obtained were noted. Average values do seem to indicate a noticeable terminal rise, as might be expected (Tables I, II, and III).

Plasma Calcium.—In all 3 groups of animals the calcium concentration in the plasma decreases during the first 24 hours of survival. Serum calcium in control wounded animals fell from a mean of 4.46 ± 0.30 mEq./L. to 3.92 ± 0.67 mEq./L. and the toxin-shocked animals from 4.48 ± 0.36 to 2.88 ± 0.30 mEq./L. The penicillin-treated wounded animals showed a drop from 4.40 ± 0.40 to 2.96 ± 0.42 mEq./L. (Tables I, II, and III). After 24 hours of survival, the calcium levels of the penicillin-treated wounded animals remained nearly constant.

Plasma Inorganic Phosphate.—A mean increase from 3.55 ± 1.14 to 5.06 ± 1.11 mEq./L. of inorganic phosphate was found in the plasma of the control animals. The toxin-shocked and penicillin-treated wounded animals did not show significant changes in inorganic phosphate levels (Tables I, II, and III). It is interesting to note that penicillin-treated animals surviving for shorter periods (24 to 30 hours) all had increased phosphate levels while the longer surviving members of the series (30 to 72 hours) show uniform levels from the time of wounding until the terminal blood sample.

TABLE I. CONTROL WOUNDED ANIMALS—SERUM ELECTROLYTES (MEQ./L.)

TIME (HOURS)	0	6	14	15 to 25	30 to 37*
Sodium	145.7 ± 9.88	145.7 ± 8.94	146.6 ± 7.76	148.1 ± 4.97	152.5
Potassium	4.5 ± 1.0	4.8 ± 1.24	4.8 ± 1.59	4.1 ± 1.01	8.7
Calcium	4.64 ± 3.0	4.12 ± 0.70	3.87 ± 0.47	3.92 ± 0.67	4.03
Inorganic Phosphate	3.55 ± 1.14	4.25 ± 1.05	4.77 ± 1.41	5.06 ± 1.11	2.57
Magnesium	1.55 ± 0.38	2.23 ± 0.48	2.71 ± 0.83	3.76 ± 0.41	3.35

*Average of 2 animals.

TABLE II. PENICILLIN-TREATED WOUNDED ANIMALS—SERUM ELECTROLYTES (MEQ./L.)

TIME (HOURS)	0	6	14	22 to 28	29 to 48	56 to 69
Sodium	143.7 ± 8.35	144.2 ± 11.21	143.6 ± 15.61	142.1 ± 22.76	138.7 ± 12.41	141.8 ± 14.04
Potassium	6.0 ± 2.49	6.2 ± 2.14	5.7 ± 1.77	5.7 ± 1.07	5.9 ± 1.73	7.8 ± 4.21
Calcium	4.40 ± 0.40	3.74 ± 0.42	3.31 ± 0.60	2.96 ± 0.42	3.84 ± 0.43	3.45 ± 0.42
Inorganic Phosphate	2.57 ± 0.92	2.81 ± 1.17	2.99 ± 1.31	3.28 ± 1.61	2.82 ± 1.11	2.54 ± 0.30
Magnesium	1.88 ± 0.22	2.45 ± 0.50	3.04 ± 0.70	3.55 ± 0.48	3.84 ± 1.09	4.57 ± 0.26

Plasma Magnesium.—All 3 groups of animals show an increase in the plasma magnesium which continues throughout the full time that the animals survive. During the first 24 hours the penicillin-treated wounded animals' magnesium levels increased from a mean of 1.88 ± 0.22 to 3.55 ± 0.48 mEq./L. Control animals had average increases from 1.55 ± 0.38 to 3.16 ± 0.41 mEq./L. The magnesium levels in the plasma of the toxin-shocked animals rose but to a lesser extent than the other groups (1.83 ± 0.14 to 2.73 ± 0.85 mEq./L.). Further information is given in Tables I, II, and III. The penicillin-treated wounded animals exhibit an interesting phenomenon regarding terminal magnesium concentrations. All animals surviving longer than 30 hours possess nearly the same terminal magnesium levels (4.80 ± 0.22 mEq./L.) despite the wide variations in the survival times (30 to 72 hours).

TABLE III. TOXIN-SHOCKED ANIMALS—SERUM ELECTROLYTES (MEQ./L.)

TIME (HOURS)	0	6	14	22 to 28
Sodium	142.9 ± 12.30	133.2 ± 11.52	148.4 ± 20.05	149.0 ± 15.69
Potassium	5.3 ± 1.98	5.0 ± 1.70	5.3 ± 2.1	5.6 ± 2.36
Calcium	4.48 ± 0.36	3.93 ± 0.30	3.68 ± 0.56	2.88 ± 0.30
Inorganic Phosphate	3.28 ± 0.43	2.53 ± 0.86	3.44 ± 1.87	3.16 ± 1.26
Magnesium	1.83 ± 0.14	2.40 ± 0.37	2.42 ± 0.78	2.73 ± 0.85

Nonprotein Nitrogen.—The nonprotein nitrogen level in all groups begins to rise immediately after wounding or toxin injection and the increment continues until the terminal state. At the end of 24 hours the nonprotein nitrogen of all groups averaged approximately 85 mg. per cent (Tables IV, V, and VI). Since the penicillin-treated wounded animals survive longer, their terminal samples are proportionately higher. From the average values, the rise in nonprotein nitrogen appears to be linear; therefore, the increase per unit of time is constant throughout the survival period. Penicillin may be said to have a permissive action in this case.

TABLE IV. CONTROL WOUNDED ANIMALS—NITROGENOUS FRACTIONS (MG. PER CENT)

TIME (HOURS)	0	6	14	15 to 25	30 to 37*
Nonprotein nitrogen	38.8 ± 4.14	51.9 ± 8.62	60.5 ± 9.89	80.68 ± 29.46	66.1
Blood urea nitrogen	20.5 ± 3.07	30.8 ± 4.84	36.8 ± 15.1	52.4 ± 30.8	37.9
Creatinine	1.14 ± 0.21	1.67 ± 0.51	1.96 ± 0.63	2.34 ± 0.95	1.35
Creatine	1.07 ± 0.45	3.53 ± 2.14	4.75 ± 2.59	6.02 ± 3.84	1.66
Amino Acid Nitrogen	5.9 ± 1.03	6.3 ± 1.14	6.4 ± 1.45	6.0 ± 2.63	5.05

*Average of 2 animals

Urea Nitrogen.—The urea nitrogen levels rise similar to the nonprotein nitrogen levels. At the end of 24 hours urea nitrogen of all groups increases from about 20 mg. per cent to nearly 55 mg. per cent (Tables IV, V, and VI). Much of the rise in nonprotein nitrogen seems to be accountable through the increase in circulating urea. Also, like the nonprotein nitrogen, the urea nitrogen levels of penicillin-treated animals show much higher terminal levels which again may be due to increased survival.

It is interesting to note that in the control samples the blood urea nitrogen represents about 70 per cent of the total nonprotein nitrogen. In the terminal

TABLE V. PENICILLIN-TREATED WOUNDED ANIMALS—NITROGENOUS FRACTIONS (MG. PER CENT)

TIME (HOURS)	0	6	14	22 to 28	29 to 48	56 to 69
Nonprotein nitrogen	36.8 ± 3.43	45.9 ± 3.25	58.2 ± 6.74	91.09 ± 18.86	120.4 ± 25.16	160.4 ± 2.45
Blood urea nitrogen	18.24 ± 4.42	28.4 ± 4.38	33.4 ± 6.61	56.1 ± 22.43	80.74 ± 28.35	117.5 ± 1.28
Creatinine	1.07 ± 0.16	1.41 ± 0.26	1.68 ± 0.44	3.15 ± 1.33	3.53 ± 0.92	5.54 ± 0.79
Creatine	1.07 ± 0.71	2.67 ± 0.30	4.44 ± 0.55	7.00 ± 3.02	9.29 ± 2.51	16.85 ± 5.18
Amino acid nitrogen	4.5 ± 2.18	3.8 ± 1.18	3.5 ± 1.32	3.9 ± 1.68	4.3 ± 0.80	5.0 ± 2.27

TABLE VI. TOXIN-SHOCKED ANIMALS—NITROGENOUS FRACTIONS (MG. PER CENT)

TIME (HOURS)	0	6	14	22 to 28
Nonprotein nitrogen	38.2 ± 3.37	49.2 ± 8.42	54.4 ± 9.69	80.1 ± 27.95
Blood urea nitrogen	19.9 ± 7.48	26.1 ± 11.39	32.0 ± 7.02	52.8 ± 20.10
Creatinine	1.22 ± 0.16	1.44 ± 0.22	1.88 ± 0.53	2.96 ± 1.08
Creatine	1.21 ± 0.10	1.81 ± 0.29	2.04 ± 1.9	7.41 ± 3.37
Amino acid nitrogen	7.6 ± 6.32	6.5 ± 3.65	4.9 ± 2.97	5.97 ± 5.97

samples from the penicillin-treated wounded animals the blood urea nitrogen makes up only about 52 per cent of the nonprotein nitrogen.

Creatinine.—The creatinine levels of the toxin-shocked and control wounded animals rise slightly from wounding until death (Table IV, V, and VI). The penicillin-treated wounded animals maintain essentially normal levels through the first 18 hours after wounding. After this period there is a quickening of the rate at which the circulating level increases. The increment is continued then until death occurs.

Creatine.—The creatine levels show some fluctuations but tend to show a constant increase from the time of wounding or toxin injection until the death of the animals (Tables IV, V, and VI).

Amino Acid Nitrogen.—The determinations of amino acid nitrogen reported here show considerable variation and therefore are not of great value. It would seem though that there is no change in the amino acid nitrogen in any of the groups in this series (Tables IV, V, and VI).

DISCUSSION

It is interesting to note that in all 3 classes of animals used in these experiments, nearly identical changes occur in the substances measured. Within comparable time intervals, that is, from 0 to 24 hours after wounding or toxin injection, the only variation seems to be differences in magnitude. The continued rise of the nonprotein nitrogen, blood urea nitrogen, creatine, and creatinine levels in the animals treated with penicillin is indicative of major impairment of renal function and/or greatly increased endogenous production. Further investigations to clarify this issue are being undertaken.

The continued rise of the nitrogen-containing components in the blood with increased survival is additional evidence that these substances are the result rather than one of the initiating factors in the shock state. Frank and co-workers[5] have dialyzed the blood of dogs subjected to hemorrhagic shock, thus maintaining the levels of these compounds within normal limits. No effect upon the progress of the shock state was found. These data are in correspondence with our findings.

In most instances in the literature amino nitrogen concentrations have been found to rise in shock. Most probably the goat is better equipped to maintain amino acid nitrogen levels than other species since our data appear to show no changes in amino acid nitrogen levels.

Animals in this type of stress appear to be able to control the level of circulating electrolytes. During the course of shock, the amounts of these elements change very slowly until terminal stages are reached.

The identical magnesium concentrations in the terminal samples of the penicillin-treated wounded animals are noteworthy. It is known that the circulating levels of ATP are greatly increased in wounded animals. Further, ATP is much more toxic in higher concentrations if magnesium ion is present in appreciable amounts. This level may then be the maximum concentration

tolerated by the animal. An alternate possibility is that this concentration of magnesium represents the maximum effort of some mechanism important in the response of the animal in stress.

CONCLUSIONS

1. Wounded animals, untreated and penicillin-treated, show increases in the nonprotein nitrogen, blood urea nitrogen, creatine, creatinine, and magnesium levels in their plasma. Toxin-injected animals show the same but generally lesser effects.

2. An increase in the inorganic phosphate levels of untreated and toxin-injected animals was noted.

3. Plasma calcium fell in all groups.

4. Plasma sodium, potassium, and amino acid nitrogen remain constant in all groups.

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A NEW PREPARATION FOR THE STUDY OF EXPERIMENTAL SHOCK FROM MASSIVE WOUNDS

VI. Paper Electrophoretic Studies of the Serum Proteins

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INTRODUCTION

NUMEROUS investigators have described changes in the serum protein constituents of animals subjected to various kinds of stress. Lewis and associates[2] have shown that there are increases in the alpha-2 and beta protein fractions in dogs that were bled and returned less than 75 per cent of their original plasma volumes. Chanutin and Gjessing[1] observed similar changes in rabbits that had been shocked by burning. A comparable increase in the alpha and beta protein fractions of the serum of mice subjected to tourniquet shock has been noted by Moore.[3] Rabbits in which shock had been induced by standard tourniquet techniques showed identical changes in the alpha fraction, but the beta fraction remained unchanged (Westphal and co-workers[5]). It seems then that there are species differences in the response to the same type of stress.

Adequate studies of the serum protein changes of animals in which shock is produced by massive soft tissue wounds is lacking. The multiplicity of the stress, that is, hemorrhage, soft tissue destruction, and bacterial contamination, would seem to indicate that such changes should occur.

EXPERIMENTAL PROCEDURE

Texas angora wether goats weighing 36 to 50 Kg. were used in this investigation. The animals were wounded by a technique previously described by Ochsner and co-workers[4] using a standard tetryl charge (0.494 by 0.795 inch) and an M36 detonator cap. This procedure produces extensive bilateral soft tissue damage with bilateral fracture of the femur.

Two groups of wounded animals were studied: (1) control animals receiving no treatment other than hemostasis and (2) animals receiving penicillin or Aureomycin before wounding and every 8 hours thereafter. The penicillin-treated animals were given dosages of 1,000,000 units of aqueous penicillin and 300,000 units of penicillin in oil. The Aureomycin-treated animals received 500

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mg. of intravenous Aureomycin per dose. In addition, a third group of unwounded animals were injected intravenously with gram-negative endotoxin in an attempt to ascertain which of the observed changes might be attributed to the metabolism of the bacteria present in the wound site. The endotoxin was prepared from a pure culture of *Escherichia coli* taken from the wound of a goat.

Ten cubic centimeter blood samples were taken within one hour before wounding or injection of the toxin; subsequent samples were taken at 6, 14, 18, and 24-hour intervals thereafter until the death of the animals. After withdrawal the blood was allowed to clot and left standing several hours until the clot had contracted. The sample was then centrifuged and the serum withdrawn and frozen until electrophoretic separation was carried out.

The serum samples were analyzed by a Durrum-type paper electrophoresis apparatus. Serum (0.01 c.c.) was placed on the paper strip. Separation was carried out at a constant voltage and pH 8.6 for periods of 10 hours. The strips were then removed from the apparatus, stained, and oven-dried. All serial samples from each animal were run simultaneously. After drying, the electrophoretic strips were scanned on a recording photometer (Analytrol) and the relative percentage of each fraction calculated.

RESULTS

Control Wounded Animals.—All of the animals in this group showed normal serum protein patterns previous to wounding. Six hours after wounding there was a slight decrease in the total protein content of the serum as determined by the total color intensity in the paper. This decrease was probably due to the initial hemorrhage and subsequent hemodilution. In this same time interval, however, the alpha-2 globulin percentage of the total protein increased from a mean of 11.8 to 18.3 per cent (Table I). Ninety per cent of the animals used in these experiments demonstrated this increase. After survival of 16 to 18 hours, there were suggestive changes in the alpha-1 and beta globulin fractions, but these did not appear to be of a significant nature.

TABLE I. RELATIVE PERCENTAGE OF ALPHA-2 GLOBULINS IN SERA OF CONTROL WOUNDED ANIMALS

NUMBER	0 HOUR	6 HOUR	TERMINAL (CIRCA 18 HOURS)
1	10	13	14
2	9	23	10
3	16	29	22
4	11	22	12
5	14	19	20
6	9	10	12
7	15	18	19
8	8	15	17
9	15	20	12
10	12	14	16
11	11	16	24
12	13	15	12
Mean	11.9	17.8	15.8

Most of the control animals showed a noticeable decrease in the albumin fraction just prior to death. A set of serial electrophoretic patterns from a typical control animal is shown in Fig. 1.

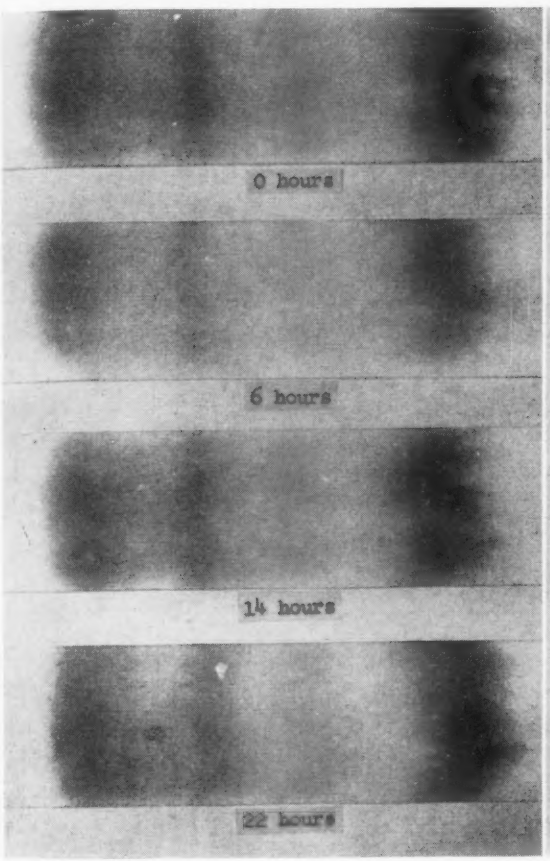

Fig. 1.

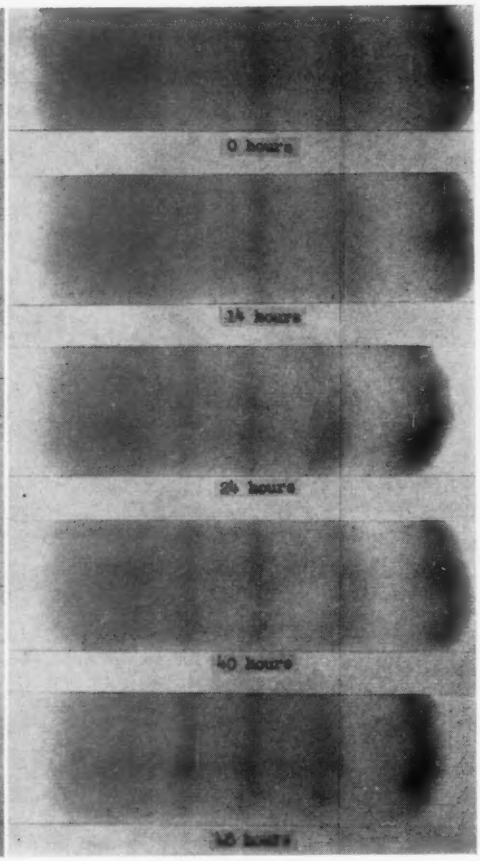

Fig. 2.

Fig. 1.—Serial paper electrophoretic patterns from the serum of a typical wounded untreated control animal.

Fig. 2.—Serial paper electrophoretic patterns from the serum of a wounded penicillin-treated animal. Note the emergence of a protein fraction in the beta region at 24 hours and the increasing density of the protein fraction at 40 and 48 hours after injury.

Antibiotic-Treated Wounded Animals.—Animals in this group showed similar changes in the total protein. At the end of about 24 hours of survival all of the antibiotic-treated animals showed changes in the region of the beta globulins. The beta stripe continued to increase in relative color density until the animals died. A comparison of the terminal values of control and antibiotic-treated animals can be found in Tables II and III. A photograph of a serial separation of the sera of a penicillin-treated animal is shown in Fig. 2. Note the changes in the beta region.

Toxin-Shocked Animals.—A small group of animals were given a lethal intravenous injection of gram-negative endotoxin. None of these animals survived past 28 hours. The endotoxin-shocked animals showed no change in the relative amounts of serum proteins present.

TABLE II. RELATIVE PERCENTAGE OF BETA-GLOBULINS IN SERA OF PENICILLIN-TREATED WOUNDED ANIMALS

NUMBER	0 HOUR	TERMINAL (CIRCA 48 HOURS)
1	6.7	27.8
2	6.9	9.3
3	5.0	14.7
4	15.3	31.4
5	8.2	25.2
6	7.1	16.4
7	6.1	8.7
Mean	7.9	19.1

TABLE III. RELATIVE PERCENTAGE OF BETA-GLOBULINS IN SERA OF CONTROL WOUNDED ANIMALS

NUMBER	0 HOUR	TERMINAL (CIRCA 18 HOURS)
1	5.2	5.6
2	18.1	10.5
3	12.0	11.1
4	16.4	19.4
5	10.3	9.6
6	7.7	9.8
7	6.2	7.2
8	8.4	14.3
9	10.5	7.2
10	7.3	10.4
11	9.3	10.5
12	8.6	3.7
Mean	10.0	9.9

Nonwounded Control Animals.—As a control measure a group of 5 animals were immobilized and given dosages of penicillin comparable to the dosages given the antibiotic-treated wounded animals. No significant changes were observed in the distribution of protein fractions in the sera of these animals.

Another group of animals were bled down to 70 mm. Hg blood pressure. Blood samples taken after 48 hours displayed suggestions of changes in the beta regions in one case; otherwise, the electrophoretic patterns were normal.

DISCUSSION

It would appear that the marked change in the beta globulin fraction observed in the penicillin-treated wounded animals probably can be accounted for by the greatly increased survival times of the animals. Several agents important in the animal's response to stress are carried in this fraction. With antibiotic therapy, endogenous mechanisms of defense become increasingly more prominent as the animal's survival time is increased.

The striking emergence of the protein stripe in the beta region deserves further attention. Our studies indicate that the normal goat shows very small beta fractions and in many cases none at all. Possibly the protein appearing in the beta area is not truly a normal beta globulin but rather a product of a severely deranged protein metabolism. Further studies are being undertaken to characterize this fraction.

The early increase in the alpha-2 globulin fraction in control animals is of interest. Apparently this increase is a direct result of the original hemorrhage and/or tissue damage at the time of wounding since a large percentage

of the immediately replaced serum protein falls in this fraction. Possibly this fraction plays a role in the anabolic processes important in the replacement of blood proteins after hemorrhage.

The lack of change in the serum proteins of animals in endotoxin-induced shock runs somewhat counter to what might be expected from other observations made in this laboratory. Studies comparing the blood chemistries of animals in wound shock and endotoxin-induced shock show similar changes in nonprotein blood constituents and serum electrolytes. It would seem that the serum protein changes are directly attributable to the massive tissue damage at the wound site.

CONCLUSIONS

1. Control wounded animals showed an early increase in the relative amounts of alpha-2 globulins in the blood serum.

2. Antibiotic-treated wounded animals which survived much longer than control animals showed a marked change in the beta globulin fraction after a survival period of 24 hours or more.

3. In animals in which shock has been induced by the intravenous injection of lethal amounts of endotoxin no changes were seen in the relative percentages of serum protein fractions.

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MALIGNANT TUMORS OF THE PARANASAL SINUSES

I. Technique of Combined Operative and Radiologic Therapy

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INTRODUCTION

RESULTS in management of malignant tumors of the paranasal sinuses by previous techniques have been disappointing. This is due, at least partially, to the late stage in which patients present themselves for treatment. A variety of approaches have been used, including surgery alone,[1, 6] radiation alone,[3] and various combinations of surgery and radiation.[2, 4, 5, 7-11] The technique to be described represents accurately directed radiation following surgery through an open cheek flap and secondary closure.

Fig. 1.—Outline of the Fergusson incision to elevate cheek flap.

TECHNIQUE

The classical Fergusson incision (Fig. 1) is used to elevate the cheek flap. When the orbit has been invaded, the superior aspect of the incision extends through the upper eyelid (Fig. 11) and the contents of the orbit are included in the resection. The bone is then sectioned with chisel and Gigli saw (Fig. 3). Careful note is made as to the site of extension of the malignancy. This site (Fig. 5) of invasion is frequently into the ethmoid or pterygoid-maxillary

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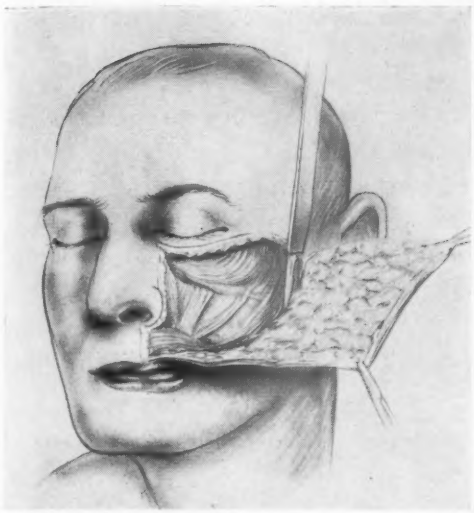
Fig. 2.



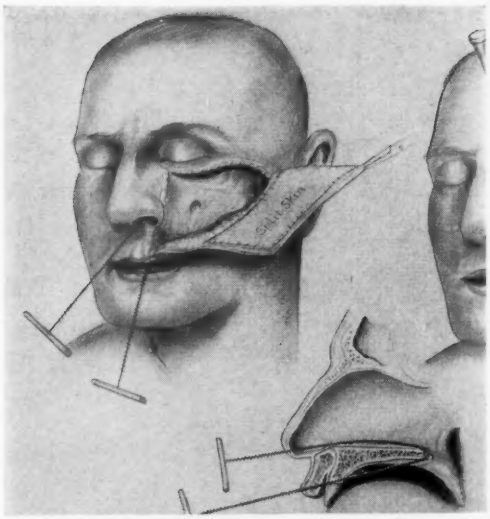
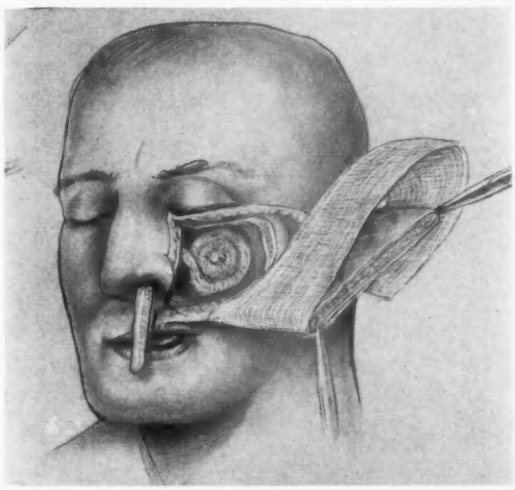


Fig. 3.

Fig. 4.



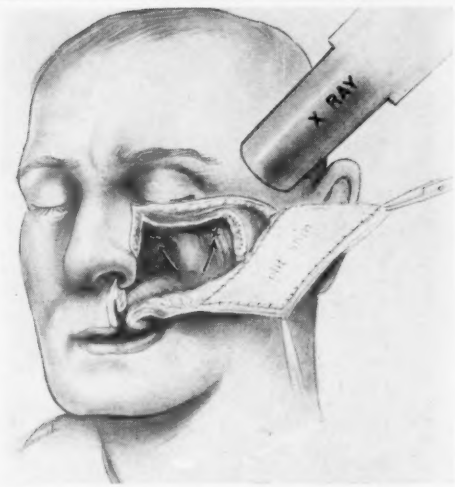
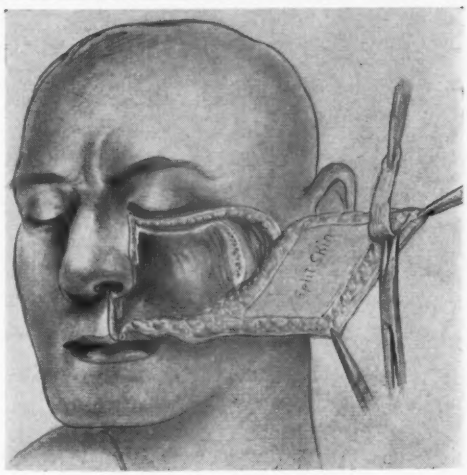


Fig. 5.

Fig. 6.



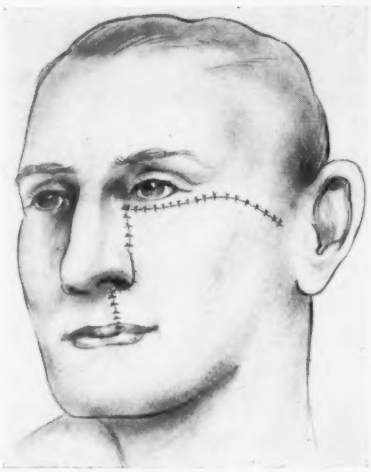


Fig. 7.

Fig. 2.—Cheek flap elevated by sharp knife dissection.

Fig. 3.—Resection of bone by chisel and Gigli saw.

Fig. 4.—Cavity packed with iodoform gauze and skin graft on inferior surface of cheek flap wrapped with Xeroform gauze and wet saline sponges.

Fig. 5.—Daily removal of antral pack and direct cone radiation to sites marked with *x*.

Fig. 6.—Secondary closure following completion of radiation, excision of the skin edges before closure.

Fig.7.—Final closure.

fossa. These areas are then heavily electrocoagulated and a pack (Fig. 4) is placed in the cavity. Split thickness graft (Fig. 3) is applied to the inferior surface of the cheek flap and fixed with catgut sutures. The skin flap, with the lined skin graft is wrapped (Fig. 4) with Xeroform and wet gauze sponges.

The day following surgery, direct cone irradiation (Fig. 5) is administered to the marked areas where there seems to be deep invasion by tumor. These areas are treated daily for one week, delivering a total tumor dose of 4,800 to 5,500 roentgens. Radiation therapy is delivered by using a 4 cm. cone or multiple cones with 250 K.V.P. and a filter of 1 mm. Cu and 1 mm. Al (half value layer 1.9 mm. Cu).

Fig. 8.

Fig. 9.

Fig. 8.—Patient, 46 years of age, with proptosis of left eye caused by tumor of maxillary sinus.

Fig. 9.—Postoperative photograph of patient seen in Fig. 8, 14 days following open-flap treatment for chondrosarcoma antrum.

Secondary closure of the cheek flap is done under local anesthesia following completion of radiation therapy. Rotation cheek flap may be necessary in those cases in which skin has been excised. The antraoral fistula is irrigated daily with hydrogen peroxide and antibiotics. Immediate application of a plastic sponge to cover the palatal defects allows the patient to eat solid food. Dental impressions are made before surgery in preparation for early fitting of oral prostheses.

RESULTS

Detailed results will be presented elsewhere, but a gross summary may be seen in Table I. There were 10 cases treated by this combined technique in the last 18 months. Seven of these are alive, with only one showing evidence

Fig. 10.

Fig. 11.

Fig. 10.—Patient, 41 years of age, with swelling of the cheek caused by adenocarcinoma of the maxillary sinus. She had had a tumor of the palate removed a year previously.

Fig. 11.—Postoperative photograph of patient seen in Fig 10, one year following open-flap treatment for adenocarcinoma of maxillary sinus.

Fig. 12.—Prosthesis applied to patient seen in Figs. 10 and 11.

of local recurrence. There has been no selection of cases. Fifty per cent of these patients showed far-advanced disease when first seen. There were no operative deaths. Three of the patients have died, one of peritonitis from strangulated hernia (6 months), one from intracranial metastases (1 year), and the third of cervical metastases, with no local recurrence (18 months).

TABLE I. TEN MALIGNANT PARANASAL TUMORS TREATED BY COMBINED RADIATION AND OPERATIVE TECHNIQUE

Deaths	
Operative	0
Late	3
(1) Strangulated hernia	6 months
(2) Intracranial metastases	12 months
(3) Cervical metastases	18 months
Average survival	10 months

DISCUSSION

Open flap treatment combines surgery and electrocoagulation followed by immediate direct cone radiation for malignant tumors of the paranasal sinuses. The advantages of this plan of therapy are: (1) It permits the most effective direct attack on these anatomically peculiarly-located tumors. (2) Direct cone radiation applies cancerocidal dosage directly to the invasion routes of the tumor cells. (3) Secondary closure results in early rehabilitation. There is minimal pain, no skin reaction, and an oral prosthesis can be fitted promptly. This permits early return to useful work. (Figs. 9 and 12).

Evaluation of results should take into consideration the condition of the patient. Arrest of cancer with the patient complaining of pain, drainage from sequestration of bone and cellulitis, and major facial defects are not very gratifying. Our patients are discharged from the hospital in 10 to 14 days without a dressing (Fig. 9) and they are able to return to useful work shortly thereafter.

We have also employed this technique in the treatment of tumors that invaded the maxillary sinus secondarily from primary tumors of the oral cavity or tumors originating from the skin of the face.

Patients with base of the skull involvement, invasion beyond the pterygoids into the nasopharynx, bilaterality of the disease, and fixed metastatic nodes of the neck are classified as inoperable.

SUMMARY

A technique is outlined for the treatment of malignant tumors of the paranasal sinuses by radiation directed to the tumor after elevation of a cheek flap. The cheek flap is subsequently sutured in position, producing an excellent cosmetic result, and early rehabilitation of the patient.

Drawings and photographs were made by Medical Photography at Veterans Hospital in St. Louis, Missouri.

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THE EFFECT OF PERIPHERAL NERVE INTERRUPTION, SYMPATHETIC PARALYSIS, AND POSTURE ON THE BLOOD PRESSURE IN THE HUMAN EXTREMITY

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THE discovery in 1628 by Harvey that blood moves in a closed circuit first awakened interest in the problem of pressure and velocity of blood flow. Approximately 100 years later, Stephen Hales[7] measured the blood pressure in the horse by allowing the blood to enter an erect tube. He also estimated the velocity of blood flow in the aorta by measuring the capacity of the ventricle and the diameter of the outflow tract.

Gaertner,[4] in 1899, described a method of blood pressure determination consisting of applying a banded pneumatic cuff to the finger which had been previously blanched. The pressure was reduced until the first color appeared in the finger distal to the cuff indicating the systolic pressure. Korotkow,[9] a Russian physician, 6 years later, described the well-known sounds which are heard as a pneumatic extremity cuff is deflated. About the same time Brodie,[1] Hewlett and Van Zwaluwenberg,[8] and others described the plethysmograph for measuring changes in the volume of an organ or extremity by enclosing it in a cup or container. Blood flows were based upon the principle that, if the venous return was occluded, any change in the volume of the part must represent the amount of blood which has entered the part during the period of venous occlusion. The development of a sensitive digital plethysmograph by Burch[2] in 1947 and the electronic pneumoplethysmograph later introduced by Winsor[12] provided a means of measuring blood pressure in the extremities utilizing the principle set forth by Gaertner with measurement of the first entrance of blood into the digit as the pressure is reduced.

MATERIALS AND METHODS

The subjects studied constituted 4 groups of patients.

1. Normal.—This group consisted of 14 patients referred for study in the vascular laboratory in whom no disease was found or in whom the vascular lesion was not related to the part studied.

2. Post Anterior Poliomyelitis.—This group consisted of 7 patients, 12 years and younger, with partial unilateral paralysis and shortening.

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3. Vasoconstrictive Disease.—This group consisted of 8 patients, 5 with acrocyanosis and 3 with cold, wet, cyanotic hands and feet. Also included in this group were 3 patients with Raynaud's disease.

4. Organic Occlusive Disease.—This group consisted of 25 patients with 12 femoral artery occlusions, 8 with iliac artery occlusion and 5 with terminal aortic occlusion.

The determinations of systolic blood pressure were made using a Winsor electronic pneumoplethysmograph.* This instrument employs the principle that 4 cm. of the tip of a digit is enclosed in an airtight cup and the volume changes are transmitted pneumatically. These pneumatic changes are transmitted to a distensible metal capsule which produces movement of the plate of a vacuum tube and hence changes current transmission. These changes are amplified and recorded by a direct writer using a heated stylus. In these studies a digital cup was sealed to the second or fourth finger or second toe using caulking compound. A 12 cm. ribbed cuff was used for all determinations except those in the thigh where an 18 cm. cuff was used. Pressure measurements were made with a venous occlusion pressure control apparatus.† This apparatus consists of a high pressure nitrogen tank with reduction valve to reduce pressure to about 15 pounds per square inch which in turn is directed into a low pressure valve which may be set to any desired pressure below 300 mm. Hg. Blood pressure was determined from any site inflating the cuff to 250 to 300 mm. Hg. The air escape pin valve was then opened and the pressure within the cuff slowly reduced until the first entry of blood or increase in size of the digit was signaled by an abrupt upward swing of the recording stylus.[13] The recording paper was in motion at 2.5 mm. per second to avoid adherence of the heated stylus to the paper.

Blood pressures in the erect position were determined by a modification of the Stead technique[3] consisting of inflation of the cuff with the patient supine and release of pressure with the patient erect. Auscultatory brachial blood pressures were taken in the conventional fashion. In the normal group comparison of the auscultatory method, the flush technique, and the plethysmographic technique at the ankle, wrist, brachium, and thigh corresponded closely (± 5 mm. Hg). All procedures were carried out at 23° to 25° C. with the patient clothed in a light hospital gown. Posterior tibial nerve blocks were carried out at the ankle behind the medial malleolus, ulnar nerve blocks at level of the median condyle of the humerus, and median nerve blocks at the wrist just medial to the tendon of the palmaris longus muscle. Stellate sympathetic blocks were performed by the anterior approach and lumbar sympathetic paralysis by the lateral approach using a single needle. Xylocaine (1 to 2 per cent) was used as an anesthetic agent. Measurements for calculated hydrostatic effect on blood pressure in the erect position were made from the fourth rib in the mid-axillary line to mid-cuff level at the ankle. This measurement was then considered as the height of a column of water and transposed to millimeters of mercury.

*Manufactured by Electro-Medical Engineering Co., Burbank, Calif.
†Manufactured by Electro-Medical Engineering Co., Burbank, Calif.

RESULTS

Effect of Peripheral Nerve Block.—

Normal subjects in the supine position showed a consistent rise in plethysmographic blood pressure measured at the ankle varying from 5 to 40 mm. Hg following posterior tibial nerve block (Table I). Two observations on femoral (lower thigh) blood pressures before and after posterior tibial nerve block showed a 40 mm. Hg rise corresponding to a 30 mm. Hg rise as measured at the ankle. A similar rise was seen following lumbar sympathetic block (Table IV). Two observations following ulnar nerve block showed a rise of 25 mm. Hg as measured at the wrist (Table III).

TABLE I. EFFECT OF POSTERIOR TIBIAL NERVE BLOCK ON ANKLE BLOOD PRESSURE

DIAGNOSIS	AGE	BRACHIAL BLOOD PRESSURE (MM. HG)	ANKLE BLOOD PRESSURE (MM. HG)	
			BEFORE	AFTER
Normal subjects				
1	59	130/80	R. 150	155
			L. 150	155
2	58	150/90	R. 120	130
			L. 120	130
3	61	132/90	R. 135	150
			L. 135	150
4	54	180/90	R. 160	190
			L. 160	200
5	45	136/80	R. 120	130
			L. 120	130
6	33	122/66	R. 95	110
			L. 95	110
7	45	124/70	R. 120	135
			L. 110	125
8	14	112/78	R. 125	150
			L. 125	150
9	34	155/100	R. 150	165
			L. 150	165
10	39	120/80	R. 135	160
11	48	160/90	R. 170	200
			L. 165	195
12	58	130/80	R. 150	180
			L. 150	180
13	46	118/70	R. 90	105
14	51	135/90	R. 180	185
			L. 180	185
Vasoconstrictives				
1	37	105/80	L. 0	90
2	20	114/70	R. 20	70
			L. 20	70
3	31	120/80	R. 120	135
			L. 120	135

TABLE I—CONT'D

DIAGNOSIS	AGE	BRACHIAL BLOOD PRESSURE (MM. HG)	ANKLE BLOOD PRESSURE (MM. HG) BEFORE	ANKLE BLOOD PRESSURE (MM. HG) AFTER
Vasoconstrictives (cont'd)				
4	54	130/70	R. 100 L. 90	125 120
5	57	140/90	R. 125 L. 125	135 135
6	30	104/60	R. 105 L. 105	120 120
7	37	124/76	R. 40 L. 40	110 115
8	37	120/90	R. 125 L. 130	160 165
Postpolio				
1	8	130/64	R. 50 L. 30	60 60
2	8	108	R. 60 L. 0	80 80
3	12	114/68	R. 100 L. 100	125 125
4	8	100/60	R. 0 L. 0	70 70
5	12	110/68	R. 90	100
6	4	120/80	R. 80 L. 110	120 120
7	22	92/70	R. 0 L. 0	90 85
Bilateral femoral occlusions				
1	69	190/70	R. 80 L. 60	80 70
2	76	150/90	R. 0 L. 0	70 70
3	60	150/86	R. 90 L. 65	100 80
4	65	162/78	R. 35 L. 80	65 110
5	79	150/80	R. 40 L. 35	50 50
6	57	124/74	R. 0 L. 0	125 100
Unilateral femoral occlusions				
1 (Right)	43	120/90	R. 70 L. 90	90 155
2 (Right)	66	160/90	R. 0 L. 90	55 120
3 (Right)	55	160/94	R. 35 L. 100	60 150

TABLE I—CONT'D

DIAGNOSIS	AGE	BRACHIAL BLOOD PRESSURE (MM. HG)	ANKLE BLOOD PRESSURE (MM. HG) BEFORE	AFTER
Unilateral femoral occlusions (cont'd)				
4 (Left)	56	124/78	R. 90	130
			L. 0	80
5 (Left)	70	162/120	R. 120	125
			L. 40	40
6 (Left)	43	136/86	R. 155	170
			L. 0	0
Terminal aortic occlusion				
1	59	122/66	R. 10	65
			L. 40	60
2	66	160/90	R. 0	55
			L. 90	120
3	62	120/80	R. 80	85
			L. 50	80
4 (Partial)	55	144/80	R. 85	95
			L. 95	130
5 (Partial)	51	110/80	R. 100	100
			L. 90	90
Bilateral iliac occlusion				
1	56	150/90	R. 30	55
			L. 80	100
2	56	175/105	R. 10	15
			L. 10	15
3	52	150/90	R. 120	120
			L. 115	115
4 (Partial)	72	200/110	R. 100	120
5 (Partial)	50	140/90	R. 100	125
			L. 110	135
Unilateral iliac occlusion				
1 (Left)	53	130/90	R. 110	120
			L. 90	100
2 (Left)	62	120/80	R. 80	85
			L. 50	80
3 (Left, partial)	63	150/86	R. 130	150
			L. 90	130

TABLE II. EFFECT OF NERVE BLOCKS ON FEMORAL AND ANKLE BLOOD PRESSURE

DIAGNOSIS	AGE	BRACHIAL BLOOD PRESSURE (MM. HG)	FEMORAL BLOOD PRESSURE (MM. HG) BEFORE	AFTER	ANKLE BLOOD PRESSURE (MM. HG) BEFORE	AFTER
Posterior Tibial Nerve Block						
Normal						
1	58	130/80	R. 165	205	R. 150	180
			L. 165	205	L. 150	180
Lumbar Sympathetic Nerve Block						
Normal						
1	43	140/90	L. 150	180	L. 100	120

TABLE III. EFFECT OF NERVE BLOCKS ON WRIST BLOOD PRESSURE

DIAGNOSIS	AGE	BRACHIAL BLOOD PRESSURE (MM. HG)	WRIST BLOOD PRESSURE (MM. HG) BEFORE	AFTER
Ulnar Median and Sympathetic Nerve Blocks				
Normal				
1 (Ulnar)	39	120/80	R. 120	145
			L. 125	150
Vasoconstrictive				
1 (Ulnar)	20	114/70	R. 70	120
			L. 20	90
2 (Median, left)	26	100/60	L. 35	100
3 (Median, right)	32	134/70	R. 120	130
Subclavian occlusion, left				
1 (Ulnar)	59		R. 125	175
			L. 0	90
Complete coaretation of the aorta				
1 (Ulnar)	18	164/80	R. 105	135
			L. 95	135
Blood pressures at ankle with posterior tibial nerve block			R. 50	85
			L. 50	80
Stellate Ganglion Block				
Raynaud's disease				
1 (Right)	26	100/60	R. 30	60
2 (Right)	23	122/76	R. 90	100
3 (Right)	46	118/70	R. 40	105

Eight patients with vasoconstrictive disease had a rise of 10 to 90 mm. Hg following posterior tibial nerve block (Table I). A similar result was seen in 3 patients in the same category following temporary ulnar and median nerve interruption (Table III).

Postpoliomyelitis patients showed a rise of 10 to 90 mm. Hg following posterior tibial nerve block with maximal effects on the involved side (Table I).

Patients with occlusive disease in the upper and lower extremities involving the aorta, subclavian, iliac, and femoral arteries on only 3 occasions failed to show a rise in pressure following ulnar or posterior tibial nerve block. Studies in one patient with coaretation of the thoracic aorta revealed rises in pressure in both upper and lower extremities (Tables I and III).

TABLE IV. EFFECT OF LUMBAR SYMPATHETIC BLOCK ON ANKLE BLOOD PRESSURE

DIAGNOSIS	AGE	BRACHIAL BLOOD PRESSURE (MM. HG)	ANKLE BLOOD PRESSURE (MM. HG) BEFORE	AFTER
Normal				
1	43	140/90	R. 135	155
			L. 135	155
Vasoconstrictives				
1	37	110/90	R. 125	160
			L. 130	165
2	26	136/72	R. 60	120
			L. 60	120
3	37	120/80	R. 0	120
			L. 0	120
4	46	118/70	R. 90	105
5 (Hypertensive)	53	160/100	R. 180	210

Effect of Sympathetic Nerve Block.—Only one normal and 5 vasoconstrictives were studied in this category following lumbar sympathetic nerve block (Table IV). Similar rises varying from 15 to 20 mm. Hg were seen. Three patients with Raynaud's syndrome were observed before and after upper dorsal sympathetic nerve paralysis and rises from 10 to 65 mm. Hg were observed (Table IV).

Effect of Sympathectomy.—Postpoliomyelitis, vasoconstrictive states, and occlusive disease showed marked rises following excision of the lumbar sympathetic chain and in one case following the removal of the upper 5 dorsal sympathetic ganglia (Table V).

TABLE V. EFFECT OF SYMPATHECTOMY ON ANKLE AND WRIST BLOOD PRESSURE

DIAGNOSIS	AGE	BRACHIAL BLOOD PRESSURE (MM. HG)	ANKLE BLOOD PRESSURE (MM. HG)	
			BEFORE	AFTER
Postpolio				
1 (Right Lumbar)	4	120/80	R. 80	125
2 (Left Lumbar)	8	106/70	L. 0	70
3 (Right Lumbar)	4½	110/70	R. 120	105
Vasoconstrictive				
1 (Bilateral Lumbar)	26	110/60	R. 60	125
			L. 60	125
2 (Bilateral Lumbar)	57	124/74	R. 0	125
			L. 0	75
3 Dorsal	25	106/60 (Wrist)	R. 30	110
			L. 25	105
Femoral occlusions				
1 (Lumbar)	55	126/74	R. 90	120
			L. 95	120
2 (Lumbar)	43	138/80	R. 145	155
			L. 70	100

Effect of Positional Changes on Blood Pressure at the Ankle Before and After Nerve Block or Sympathetic Paralysis.—

Before nerve block: This group constituted normals and occlusive disease. In general, with elevation of the legs toward the "L" position to 32.5 or 65 cm. above the heart, there was a drop in measured pressure proportional to the height of the elevation. The erect position produced marked rises. Variances were small with the exceptions of Case No. 3 (normal) and one observation in a patient with Buerger's disease (Table VI).

After nerve block: Here, the changes were again proportional to the calculated height with some being higher than the calculated. Again Case No. 3 (normal) showed wide variance. In general, the changes in the erect position before and after block tended to be less than the calculated pressure (Fig. 1).

Control Study.—One patient without demonstrable vascular disease other than a mild hypertension was studied before and after posterior tibial nerve block with 2 per cent Xylocaine on one side and before and after nerve infiltration with physiologic saline on the other (Table VII), showing that the injection

TABLE VI. EFFECT OF POSITIONAL CHANGES ON ANKLE BLOOD PRESSURE BEFORE AND AFTER SYMPATHETIC PARALYSIS AND POSTERIOR TIBIAL NERVE BLOCK

DIAGNOSIS	ANKLE BLOOD PRESSURE AT VARIOUS POSITIONS						
	SUPINE	32.5 CM. ELEV.		65 CM. ELEV.		ERECT	
	ACTUAL	CALC.	ACTUAL	CALC.	ACTUAL	CALC.	ACTUAL
A. Before							
Normal							
1	R. 135			R. 90	100	R. 205	210
	L. 135			L. 90	100	L. 205	210
2	R. 135					R. 230	210
	L. 135					L. 230	210
3	R. 180	R. 158	150	R. 135	145	R. 258	210
	L. 180	L. 158	150	L. 135	145	L. 258	210
Occlusive disease							
1	R. 110					R. 208	175
	L. 155					L. 243	210
2	R. 110	R. 88	100	R. 65	80	R. 144	165
	L. 90	L. 68	60	L. 45	60	L. 169	150
3	R. 130					R. 214	210
	L. 130					L. 214	210
4 (Aortic)	R. 130	R. 108	100	R. 85	90		
	L. 130	L. 108	100	L. 85	90		
Buerger's disease							
1	R. 80	R. 58	45	R. 35	0		
B. After							
Normal							
1 (left lumbar block)	R. No block						
	L. 155			L. 110	120	L. 225	230
2 (Posterior tibial block)	R. 165					R. 250	250
	L. 165					L. 250	250
3 (Posterior tibial block)	R. 185	R. 163	155	R. 140	150	R. 265	215
	L. 185	L. 163	155	L. 140	150	L. 262	215
Occlusive disease							
1 (Iliac occlusion posterior tibial block)	R. 120	R. 98	105	R. 75	90	R. 190	180
	L. 100	L. 78	90	L. 55	65	L. 180	160

Elev. = elevation above heart. Calc. = calculated.

TABLE VII

Diagnosis: Hypertension
Height: 6′ 1.5″

Age: 56
Brachial blood pressure: 160/110 (auscultatory)

A. Study of the effect of positional changes on blood pressure measured in millimeters of mercury at the right ankle before and after posterior tibial nerve block with 2 per cent Xylocaine solution.

	Before	*After*
Supine position	160	200
32.5 cm. elevation	150	180
65 cm. elevation	130	150
Erect position	210	250

B. Study of the effect of positional changes on blood pressure in millimeters of mercury at the left ankle before and after posterior tibial nerve infiltration with physiologic saline solution.

	Before	*After*
Supine position	160	160
32.5 cm. elevation	150	150
65 cm. elevation	130	130
Erect position	210	210

per se has no effect on the central pressure or the pressure as measured at the ankle. The usual rise in pressure was seen after the posterior tibial block.

DISCUSSION

The distribution of blood is carried out by the larger arteries and their branches but the effective physiologic changes pertaining to the metabolism of the cell occur in the capillary bed. It is at this point that the actual change of nutritive and waste substances takes place. These changes occur in relation to the oncotic pressure as balanced against the intraluminal capillary pressure in the presence of a semipermeable membrane. Survival of the cells is concerned with pressure and volume flow in these capillaries. It is therefore important to have some idea of the controlling mechanisms of this pressure and flow. A previous communication by Leeds, Freeman, and Gilfillan[10] concerning

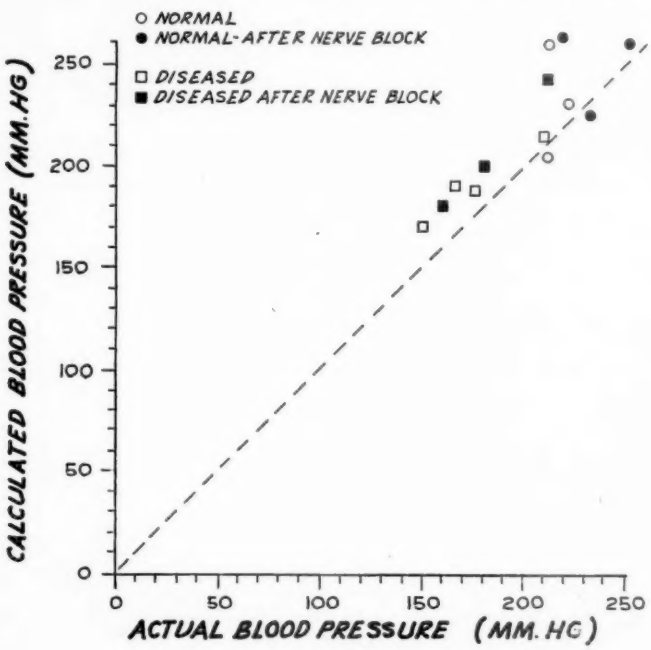

Fig. 1.

the blood pressure in the minute vessels of the human skin reveals that after sympathectomy there is almost always a definite increase in the pressure in the small vessels of the sympathectomized extremity. This information was obtained using an elevation reactive hyperemia method of estimating capillary pressure.[5] It was realized at the time that we were not studying fluid movement in rigid tubing but rather that we were dealing with plastic flow terminating in extremely fine capillary vessels, and that as such we were concerned with a situation in which arterial venous pressure differences between the artery and vein supplying a capillary network must be at least 10 and in many regions 20 to 40 mm. Hg before the blood begins to flow through the capillaries.[6] However, in measuring the pressure in vessels the size of the anterior and posterior tibial at the ankle, Bernoulli's law probably more closely applies.

Release of sympathetic control and an increase in diameter would increase the lateral pressure to account for the pressure increases in these larger vessels following sympathetic paralysis or partial sympathetic paralysis with peripheral nerve interruptions.

The changes in pressure on variation of posture seemed to be totally hydrostatic or gravimetric as is indicated by the comparison to calculated pressures for the same position. These pressures are probably slightly modified by visceral reflex nervous control. The increase of blood pressure following sympathetic paralysis and the increase in pressures on postural change probably account for the relief of ischemic pain seen at times following sympathectomy and on assuming the erect position. The success in the treatment of gangrenous lesions of the feet and legs described by Foley may also be on this basis.[3] Scheinberg and co-workers[11] have shown that the inflow of blood into an extremity is greatest when the veins are empty. This, coupled with the knowledge that the blood pressure is increased with the legs in a dependent position, probably accounts for the success of the oscillating bed wherein the venous blood is drained on elevation following which the extremity is placed in a dependent position and allowed to refill. The high pressures observed with patients erect calls to mind the possibility of this being one of the mechanisms involved in the filtration theory of the causation of atherosclerosis.

SUMMARY

A series of observations have been made on the blood pressure as measured at the ankle by the plethysmographic technique. These blood pressures are increased by sympathectomy, peripheral nerve interruption, and changed by posture.

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EFFECTS OF SYMPATHECTOMY ON BLOOD TURNOVER RATES IN MUSCLE AND BONE

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THE effects of lumbar sympathectomy on blood flow in the lower extremity are still disputed, despite many years of exhaustive study and discussion.[3-6, 10, 14, 16, 17, 19, 21, 23, 27] It is generally agreed that total limb flow is greater after the operation.[3, 6, 19, 23, 27] Debate hinges on the question whether increased skin flow accounts for all or most of the change.[19, 23, 27] The worth or worthlessness of sympathectomy in treating peripheral vascular disease depends upon the answer to this key question, since the usual aim of treatment is to deliver more oxygen to the muscles, not to the skin. That varying, indeed contradictory, answers have been given is attributable in part to the lack of a reliable method for comparing flow through the muscle, bone, and skin compartments. The commonly used techniques of thermometry,[3, 23] plethysmography,[1, 5, 19, 27] and bleeding[3, 23] measure the sum of flow in all 3 compartments, in variable degrees. Carbon particles[28] and radiopaque materials[20, 24] have been used for qualitative studies of bone circulation. Radioisotopes make possible a sharper attack on the problem. Kety[7, 8] studied local clearance rates of injected radiosodium from muscle, skin, and other tissues and showed that these rates are proportioned to blood flow. Petrakis[15] adapted this technique to the bone marrow and observed that marrow and muscle clearance rates of radioiodide were similar except in some leukemic patients, in whom the clearance was considerably faster. These clearance rates are dependent upon diffusion factors and the size of the extravascular space as well as blood flow through the region.[8]

We have used a similar technique for studying the effect of lumbar sympathectomy on muscle and bone flow in the dog's hindlimb, but with modifications that eliminate the diffusion and extravascular factors. Our tracer was an isotopically labeled dye, I^{131} rose bengal, which is bound to plasma proteins[18] and does not leave the vascular bed until it reaches the liver, where it is rapidly removed from the circulation.[11, 22] This material was injected by turns into the tibial marrow and the femoral artery, with a gamma ray counter placed over the tibia and over the fleshy part of the thigh, respectively (Fig. 1). Under these conditions, the clearance rate is the same as the blood turnover rate: The number of times each minute that the local blood pool is replaced by fresh

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blood.[9, 12, 13] Because the bulk of muscle in the dog's thigh is much greater than that of the other tissues (skin and bone), the turnover rates measured at the thigh were assumed to be largely determined by muscle flow.

METHOD

Seventeen healthy mongrel dogs, weighing from 6 to 12.8 Kg., were anesthetized with intravenous Nembutal (30 mg. per kilogram of body weight) and subjected to lumbar sympathectomy through the transperitoneal approach. The lumbar chains were resected as completely as possible from the level of the diaphragmatic crux down to the iliac veins. In 13 animals the procedure was unilateral, in 4 bilateral.

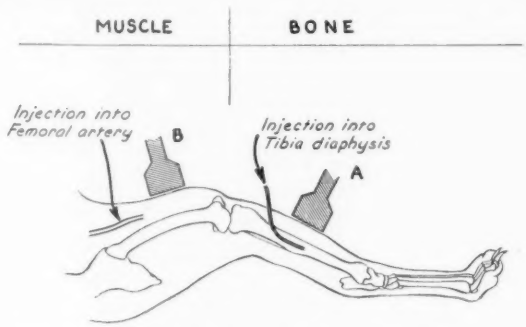

Fig. 1.—Injection sites and placement of radiation detector for measurement of flow in bone (*A*) and muscle (*B*).

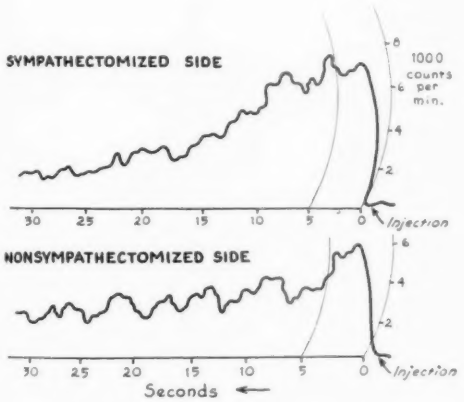

Fig. 2.

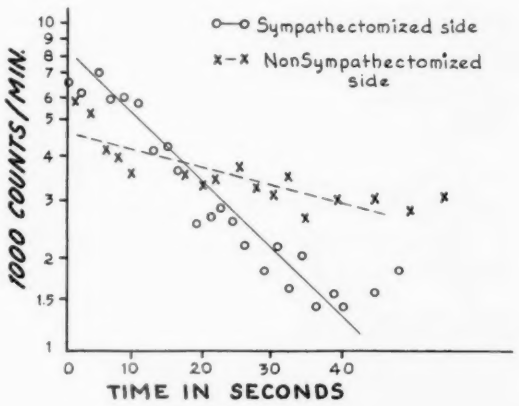

Fig. 3.

Fig. 2.—Dilution curves (Esterline-Angus records) obtained after tibial injection of I^{131} rose bengal, comparing sympathectomized and nonsympathectomized limbs.

Fig. 3.—Semilogarithmic plot of dilution curves in Fig. 2, showing faster turnover rate (steeper slope) in sympathectomized limb. Turnover rates are 2.6 and 0.7 per minute in the sympathectomized and nonsympathectomized limbs, respectively.

As shown in Fig. 1, injections for muscle turnover rate were into the femoral artery; for bone, the dye was injected through a fine polyethylene catheter that had been slipped through a burr hole in the tibial diaphysis. Five to 30 μc of I^{131} rose bengal in 0.25 to 1.00 c.c. made up each dose. The radiation detector was a lead-shielded NaI (thallium-activated) scintillation counter with count rate meter and Esterline-Angus recorder.

Typical dilution curves are shown in Fig. 2. Prior to recirculation, the disappearance is exponential and so makes a straight line on a semilogarithmic plot (Fig. 3). The slope of this line is the blood turnover rate.

RESULTS

Table I shows turnover rates in thigh and tibia of dogs that had unilateral sympathectomy. Only one animal (No. 7) had less bone flow on the operated side than the unoperated side; one other (No. 5) had the same. All the rest had higher turnover rates, in both thigh and tibia, on the sympathectomized side. The mean increase (with standard deviation) is 66 ± 30 per cent for thigh and 53 ± 34 per cent for tibia. On the day of surgery, the average turnover rate was only 27 per cent higher in the sympathectomized limb (combining muscle and bone data). One to 8 weeks later it was 90 per cent higher. Corresponding turnover rates in thigh and tibia were remarkably similar.

TABLE I. UNILATERAL SYMPATHECTOMY

DOG	TIME AFTER SYMPATHECTOMY	TURNOVER RATES (MIN.$^{-1}$)				DIFFERENCE	
		CONTROL		SYMPATHECTOMY			
		THIGH	TIBIA	THIGH	TIBIA	AMOUNT	PER CENT
1	1 hour	1.5		1.8 1.7		0.25	17
	1 week		1.9		3.0	1.1	58
	10 days	1.9		2.9		1.0	53
2	1 hour	1.0		1.5		0.5	50
			1.1		1.4	0.3	27
3	1 hour	2.2		2.5		0.3	14
			2.6		3.1	0.5	19
4	1 hour	1.5		2.7		1.2	80
			1.9		2.1	0.2	11
5	1 hour		2.2		2.2	0.0	0
6	2 days		1.0		1.2	0.2	20
7	3 days		1.8		1.3	-0.5	-28
8	1 week		0.7		1.7 1.6	0.95	140
9	4 weeks	1.5		3.0		1.5	100
			1.7		3.1	1.4	82
10	6 weeks	1.5		2.5		1.0	67
			1.0		2.2	1.2	120
11	6 weeks	0.5		1.0 1.4		0.7	140
			0.4		1.1	0.7	175
12	8 weeks	1.9		2.3 2.1		0.3	16
			1.5		1.6	0.1	7
13	8 weeks	1.5		3.3		1.8	120

TABLE II. BILATERAL SYMPATHECTOMY

DOG	TIME AFTER SYMPATHECTOMY (WEEKS)	TURNOVER RATES (MIN.$^{-1}$)			
		RIGHT		LEFT	
		THIGH	TIBIA	THIGH	TIBIA
14	4	3.3	3.5	3.2	3.1
15	5	2.8	2.6	2.7	2.8
16	8	2.5	1.6	2.4	1.8
17	14		2.7		2.8
					2.7

The results on 4 dogs that had bilateral sympathectomy are shown in Table II. The general effects of sympathectomy, as observed in these experiments, are summarized in Table III. In the absence of an intrinsic control, the mean turnover rates in bilateral sympathectomy (2.8 for thigh and 2.6 for tibia) are compared to the average control limb in unilateral sympathectomy (1.5 for thigh and tibia).

TABLE III. EFFECTS OF SYMPATHECTOMY
(AVERAGE VALUES)

	EXCESS FLOW IN OPERATED LIMB (PER CENT)	
	THIGH	TIBIA
Unilateral sympathectomy	66	53
Day of surgery	40	15
1-8 weeks later	83	97
Bilateral sympathectomy		
4-14 weeks after surgery	87	73

Since all measurements on the bilaterally sympathectomized animals were made a month or more after surgery, these values are roughly comparable with the "late" values in the group that had unilateral sympathectomy, and the figures are not significantly different for the 2 groups. This suggests that in the dog, at least, unilateral sympathectomy improves the circulation of a single limb just as much as bilateral sympathectomy. In man, Webber[26] failed to find any evidence of cross-communications between the left and right lumbar sympathetics.

DISCUSSION

These studies demonstrate unequivocally that circulation in muscle and bone of an extremity is augmented following lumbar sympathectomy. Since the measurements were made on healthy anesthetized dogs, it would of course be hazardous to try to apply the results to human patients with peripheral vascular disease. We do intend to apply the method to studying patients before and after sympathectomy. Our original aim was to differentiate blood turnover rates in muscle, bone, and skin. We are just beginning to investigate skin flow by means of beta-emitting isotopes.

The close correlation between thigh and tibial blood turnover rates is rather surprising if one considers the different functions of muscle and marrow, but Petrakis[15] had similar results in patients, and the tibial blood supply is interdependent with that of the thigh via the epiphyseal, periosteal, and nutrient

arteries. Petrakis showed that the marrow circulation may increase greatly in leukemia. The comparative effects of exercise on bone and muscle would be of interest.

The large increase in flow between the immediate postoperative period and the period up to 2 months later is perhaps due to progressive opening of the collateral bed, once the normal vasoconstricting sympathetic impulses have been stopped.[25]

SUMMARY

Blood turnover rates were measured in the thigh and tibia of dogs that had unilateral or bilateral sympathectomy. The corresponding rates in thigh (largely muscle) and tibia were almost identical. Average turnover rate in the sympathectomized limb was 27 per cent higher than that in the control limb one hour after surgery and 90 per cent higher 1 to 8 weeks later. In animals that had bilateral sympathectomy, no measurements were made on the day of surgery; later blood turnover rates were the same, on the average, as the later values with unilateral sympathectomy.

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OPERATIVE DECOMPRESSION OF INTESTINAL OBSTRUCTION BY LONG-TUBE JEJUNOSTOMY

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DECOMPRESSION of distended small intestine prior to surgery for mechanical obstruction is indicated whenever possible. Under certain circumstances, however, decompression by nasogastric intubation may not be successful. A noncooperative or irrational patient may either prevent the insertion of a tube or withdraw it once it has been passed. Rarely, the coexistence of pyloric or duodenal obstruction may preclude passage of a tube into the small intestine. In late obstructions the tube may not readily transverse an atonic small intestine, and valuable time may be lost in futile attempts at intubation. In the presence of strangulation obstruction, operation must be performed without delay—hence without the opportunity for long-tube decompression. For these reasons the surgeon must always be prepared to deal effectively with distention of the small intestine at operation.

The wall of the obstructed intestine is often too thin and friable to be manipulated with impunity. A search for the obstructing point by uncoiling loops of distended bowel may inflict additional damage to the weakened intestinal wall and result in perforation and leakage. Primary resection and anastomosis of an obstructed, distended segment is fraught with danger since sutures will not hold in an edematous, thinned-out bowel wall. Evacuation of intestinal contents proximal to the obstruction restores tonicity of the bowel wall by improving its circulation and promoting contraction of its smooth muscle. Surgical manipulations, including anastomoses, then become less hazardous. Improvement in circulation and restoration of muscle tone of the bowel wall also promotes earlier resumption of normal intestinal activity and hastens the patient's postoperative recovery. For these reasons it is desirable that the contents of the obstructed small intestine be removed as completely as possible at the time of surgery.

Currently accepted methods of decompressing the distended small intestine at operation include: (1) multiple needle aspirations of distended loops, (2) inlying short catheter enterostomy,[3, 4, 8, 12] (3) aseptic decompressive suction enterotomy,[1, 12] and (4) introduction of the Grafton Smith tube into the intestine via the nasogastric route by means of a flexible stylet.[9, 12]

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Multiple needle aspirations are traumatic, require extensive manipulation of each distended loop, and are ineffectual in removing a large quantity of the bowel contents. This procedure is best used only for decompressing a single loop preliminary to inserting a suction catheter.

The inlying short catheter jejunostomy does not consistently decompress all dilated loops and may not permit sufficient decompression at the time of surgery to allow a direct attack on the obstructing process.

Aseptic decompressive suction enterotomy, accomplished by the introduction of a catheter through the side arm of a suction trocar is a widely used procedure. It is preferable to a single short catheter enterotomy when complete evacuation is desired, but this may require multiple enterotomies. To accomplish decompression through a single enterotomy for a surgical procedure in a low obstruction, the enterotomy should be made in a distended loop near the obstruction. This may require undue handling of distended bowel if the obstructed point is not readily recognizable.

Introduction of a Grafton Smith tube[9, 10] through the nose and guided into the intestine by the anesthetist with the aid of a stylet is strongly advocated by Wangensteen[12] as the currently preferable method of decompression at surgery. We have had no experience with this tube, but the technique is commendable inasmuch as an enterotomy is avoided. General use of this technique is restricted, however, unless personnel other than the surgical team skilled in its performance is available in the operating room.

Direct jejunostomy without the use of a catheter[2, 6] and the traumatic Monks-Moynihan maneuver[7, 11, 12] are undesirable procedures for intestinal decompression. Direct jejunostomy gives incomplete decompression at the time of surgery, creates problems in the management of an open fistula postoperatively, and requires secondary closure. The Monks-Moynihan technique involves excessive handling of distended bowel during the process of intestinal stripping over a rigid metal tube.

We have devised and used a method which decompresses the small intestine by long-tube jejunostomy. We feel this is preferable to any of the above enterotomy techniques because: (1) it is relatively atraumatic, since the enterostomy may be done in the highest or presenting jejunal loop before searching for the point of obstruction, (2) it effectively decompresses the entire small intestine in a few minutes' time through a single enterotomy, (3) it allows suction to be maintained at any desired level during the remainder of the operation and prevents pooling of intestinal contents near the operative site, (4) it permits a long tube to remain in the lumen of the bowel for continued decompression in the postoperative period and serves as an intraluminal splint which may prevent kinking of intestinal loops,[13] and (5) when indicated in certain unusual circumstances, it may be utilized as a feeding jejunostomy during convalescence by simply adjusting the position of the tube.

Our technique is as follows (Fig. 1). A sterile single lumen, long intestinal tube with a mercury-weighted balloon (of the Cantor or Harris type) is introduced through a high jejunotomy by either a simple incision or through a trocar.

Spillage is prevented by snug traction on a purse-string suture placed in the jejunal wall prior to making the enterotomy. Suction applied to the tube empties the most proximal jejunal loop. Additional length of tube is guided through the jejunotomy and, assisted by the weight of the mercury, passes into the next distended loop. As each loop is evacuated, it is gently gathered on the tube. Trauma to the intestinal wall is minimized since manipulation of the intestine involves only decompressed segments. Successively all loops of the intestine down to the point of obstruction are decompressed in this manner.

Fig. 1.—Long-tube jejunostomy as it appears at completion of operation. The distal end of the tube is in the terminal ileum. The proximal end of the tube emerges from a stab wound in the left upper quadrant and is attached to suction.

The enterostomy is inverted around the tube with the previously placed purse-string suture. Omentum is interposed between the jejunum and abdominal wall. The proximal end of the tube is brought through a stab wound in the left upper quadrant and fixed with a suture in the skin. Suction on the tube may be continued throughout the operation, and decompression is maintained postoperatively. The tube is removed when intestinal activity has resumed and decompression is no longer necessary. The jejunostomy closes spontaneously.

CASE REPORTS

CASE 1.—J. S., a 63-year-old white man, was admitted to the Syracuse Veterans Administration Hospital on Aug. 19, 1953. He was known at least 3 years previously to have a duodenal ulcer. For 9 months prior to admission his ulcer symptoms had steadily progressed with increasing epigastric pain, nausea, and anorexia. For a month he had frequent vomiting and had lost 15 pounds. Physical examination revealed an elderly man

with signs of recent weight loss and severe dehydration. Hematocrit was 28 per cent. Gastrointestinal x-ray demonstrated an acute penetrating duodenal ulcer with pyloric obstruction and gastric retention. After 3 weeks of unsuccessful medical management, surgical consultation was obtained because of cramping periumbilical pain and absent flatus for 24 hours. At this time the patient's abdomen was distended, tympanitic, and nontender. There was classical intestinal colic synchronous with active peristaltic rushes. Roentgenograms showed multiple small bowel loops with air-fluid levels. Preoperative intestinal decompression was not possible because of the pyloric obstruction. At operation a perforated appendix was found with a large inflammatory mass. The appendix was removed. About 18 inches of the terminal ileum was involved in the pericecal inflammatory mass with obstruction of the small intestine at this point. A side-to-side ileotransverse colostomy was performed to circumvent the obstruction. For decompression of the small bowel, a jejunostomy was made about 8 inches distal to the ligament of Treitz and a Cantor tube was inserted into the bowel. The tube was passed into the ileum to a point just proximal to the ileotransverse colostomy, decompressing the intestine with suction as it was advanced. Purse-string sutures were used to invert the jejunostomy, and the proximal end of the tube was brought out through a stab wound in the skin. (In this instance the tube was not inserted until after the surgical procedure was completed, because the idea of utilizing this method of decompression occurred to us at this time.) Suction was maintained postoperatively on both nasogastric and intestinal tubes. On the eighth postoperative day, the jejunostomy tube was withdrawn to the upper jejunum and used for feeding since the patient's pyloric obstruction was as yet unrelieved. Both gastric aspirate and supplementary feedings were administered through the tube, thus simplifying the management of the patient's fluid, electrolyte, and nutrition requirements. The patient gained 7 pounds during the following 3 weeks, at which time a subtotal gastrectomy was performed. The jejunostomy tube was removed on the fifth postgastrectomy day. Further convalescence was uneventful. Four-year follow-up has shown no intestinal complications and a good result from gastrectomy.

CASE 2.—R. C., a 75-year-old white man, entered the Syracuse Veterans Administration Hospital on Sept. 3, 1953, with a 6-hour history of cramping abdominal pain, nausea, and vomiting. Physical examination revealed diffuse lower abdominal tenderness, muscle spasm, and absent peristalsis. On rectal examination, a tender extraluminal mass was felt high in the pelvis above the bladder. The diagnosis was either acute appendicitis or acute sigmoid diverticulitis. At operation, the appendix appeared to be inflamed and was excised. However, careful inspection of the removed appendix showed no suppuration consistent with the patient's clinical course and the amount of purulent exudate in the lower abdomen. Further exploration revealed an inflammatory mass of the sigmoid colon about 12 cm. in diameter to which a segment of ileum was adherent. This caused a partial obstruction of the ileum about 8 inches from the ileocecal junction. Because of the partially obstructing mass in the sigmoid colon and the fresh appendiceal stump, a transverse colostomy was performed. It was felt that the partial small bowel obstruction could be treated by nasogastric intubation. Postoperatively, the patient became delirious and repeatedly removed the Cantor tube which had been passed by the nasogastric route after the above operation. All attempts at intestinal decompression failed. By the second postoperative day, the patient had abdominal distention. During an episode of vomiting a loop of small intestine eviscerated through the colostomy incision and operation became imperative. At operation, a long-tube jejunostomy of the type we have described was performed in order to decompress the small intestine and permit its replacement into the abdomen. Decompressive suction was continued postoperatively. By the fifth day after the second operation the patient was having colostomy movements, was afebrile, and convalescing normally. The jejunostomy tube was removed on the seventh day. One month later a combined abdominoperineal resection was performed for carcinoma of the sigmoid with adherence to the bladder. The patient survived comfortably for 3 years, then died of recurrent cancer.

CASE 3.—K. P., a 23-year-old white man, was admitted to the Syracuse Veterans Hospital on Nov. 4, 1955, with a 14-hour history of left paraumbilical pain accompanied by nausea, vomiting, severe dehydration, subnormal temperature, shock, and oliguria. His abdomen was tense, distended, and tympanitic, with absent peristalsis. Roentgenograms showed distended small bowel loops with air-fluid levels and no gas in the colon. A diagnosis of strangulation obstruction was made. Within 45 minutes, 1,500 c.c. of normal saline was administered intravenously which restored urinary output and normal blood pressure. The stomach was aspirated of 1,000 c.c. of material resembling small bowel contents. At operation a volvulus of the entire small bowel mesentery was found; the extremely elongated mesentery was twisted on itself in a clockwise direction for 2 complete turns. The wall of the bowel was severely congested and bluish purple in color, with hemorrhages and erosions of the serosa. There was no pulsation of the mesenteric vessels. A small stab incision was made in the upper jejunum, and a Cantor tube was threaded through the lumen of the bowel to the lower ileum. Suction was applied to the tube as it was manipulated through the intestine and the entire small bowel was quickly and completely decompressed of air and fluid. As this was being done, it was a simple matter to release the volvulus by reversing its turns. After release of the volvulus and decompression of the bowel, the intestinal wall rapidly changed color toward normal with a reactive hyperemia in its most severely damaged portions. Some areas of discoloration and questionable viability persisted, but these areas were too scattered and extensive to consider resection. Postoperatively the patient had fever, prolonged ileus with nonpropulsive peristalsis, intermittent small watery stools, and copious drainage from the long-tube jejunostomy for 10 days, presenting a problem in fluid and electrolyte replacement. It was our feeling that this dysfunction was related to the severely damaged bowel consequent to the prolonged strangulation. The jejunostomy tube was clamped on the eleventh postoperative day and removed on the thirteenth day. Convalescence progressed normally thereafter.

CASE 4.—The same patient in Case 3 was readmitted March 27, 1956, with an 8-hour history of periumbilical pain accompanied by nausea and vomiting for 4 hours. He presented the same picture of severe dehydration and small bowel obstruction as on the previous admission, except that he was not in shock. At operation there was again a volvulus of the entire small bowel with the exception of the distal 3 or 4 feet of ileum. There was marked distension of the small intestine and its wall was bluish purple in color. There was no pulsation in the mesenteric vessels. Reduction of the volvulus resulted in some improvement in color of the bowel wall, but there was persistent cyanosis from compression of the venous return by the intestinal distention. A Cantor tube had been inserted by the nasogastric route prior to surgery but was still in the stomach. At operation it could not be manipulated through the pylorus. Therefore, a stab wound was made in the upper jejunum and a Cantor tube was threaded down the entire small bowel to within 8 inches of the cecum. Approximately 2,000 c.c. of fluid were aspirated during passage of the tube. After decompression, the color of the bowel immediately improved, pulsations were evident in all portions of the intestine, and the intestine was considered completely viable. During decompression, the patient's pulse rate decreased significantly from 160 to 120 per minute. Normal intestinal activity resumed on the second postoperative day, at which time the Cantor tube was clamped intermittently. It was permanently clamped on the fourth postoperative day and subsequently removed. The patient had an extremely benign course following this operation and presented no problem in management other than correction of his initial fluid and electrolyte deficits. Because this catastrophic event had occurred twice within 5 months, an elective mesenteropexy was performed 3 months later by plicating mesentery and suturing it to the psoas muscle. It was striking that at both the second and third operations there was complete absence of intra-abdominal adhesions between adjacent loops of bowel or between bowel and parietal peritoneum. This lack of adhesion formation was undoubtedly the factor which permitted the volvulus to recur. There has been no recurrence since the mesenteropexy.

CASE 5.—F. R., a 39-year-old white man, was admitted to the Syracuse Veterans Administration Hospital on Nov. 17, 1957. He had had a subtotal gastrectomy for duodenal ulcer 3 years previously. Four days prior to admission there was gradual onset of sharp cramping pain in the left lower quadrant of the abdomen, radiating across the entire lower back. He became anorexic without vomiting and had no bowel movement nor passage of rectal gas for 4 days.

The patient was afebrile with normal pulse rate on admission. Physical examination revealed moderate dehydration, abdominal distention and tympany, and absent peristalsis. Abdominal tenderness was a variable finding: at times not present, at other times diffuse, most often detectable in left lower quadrant and suprapubic region. The white blood cell count was 5,400/mm.^{3}, hematocrit 54 per cent, serum amylase 80 mg. per cent, and urinalysis normal. X-rays of the abdomen showed dilated small bowel loops with fluid levels with no gas in the colon. Abdominal paracentesis yielded yellow serous fluid with alkaline reaction, no amylase activity, a small number of lymphocytes, and no bacteria.

After catheterization of the bladder with removal of 1,000 c.c. of urine, suprapubic dullness and tenderness were relieved and the patient's abdominal pain completely disappeared. A few hours after admission temperature rose to 102° F. with pulse rate of 120. WBC count remained low, 4,200/mm.^{3} Abdominal tenderness recurred and was consistently in the left lower quadrant.

Preoperative preparation included administration of 5 L. of fluid (3 of saline and 2 of glucose in water) and insertion of a long intestinal (Cantor) tube by the nasogastric route. The tube went into the afferent limb of the jejunum and drained a small amount of normal-appearing upper intestinal fluid. It would not progress down the efferent limb, never drained fluid typical of intestinal obstruction, and did not reduce the abdominal distention. Therefore, operation had to be performed without the benefit of preoperative decompression.

At operation the jejunum was found adherent to the anterior abdominal wall at a point about 3 feet below the ligament of Treitz. Another adhesion provided fixation of the distal ileum. Almost all of the small bowel between these 2 points was torted 180 degrees around the proximal adhesion. The intestinal wall was viable in all areas. The adhesions were lysed and the volvulus was reduced. Release of the volvulus effected only a small reduction in the distention of the bowel as gas escaped into the colon. A long-tube jejunostomy, as we have described, was performed through a stab wound in the proximal jejunum and passed into the ileum. During the passage of the tube, 1,000 c.c. of fluid plus a large amount of air was evacuated and very effective decompression of the intestine was obtained.

There was drainage through the long-tube jejunostomy of 1,350 and 1,100 c.c. during the day of operation and the first postoperative day. Drainage was 450 c.c. on the second day and decreased daily to 80 c.c. on the fifth day. The tube was clamped on the sixth day and removed on the ninth day. On the second postoperative day intermittent peristalsis appeared and a formed stool was passed. The patient began oral intake on the seventh day and his recovery was uneventful from that time, except for a minor wound infection.

SUMMARY

Dilated obstructed small intestine should be decompressed when encountered at surgery. A technique is described for decompression of such obstructed small intestine using a long intestinal tube introduced through a jejunostomy. We have used this method with gratifying results in patients who presented distinctive and difficult problems in the management of their obstruction. Intestinal decompression is easily achieved at the time of surgery by this method, facilitating manipulation and anastomoses of the bowel. Convalescence appears

to be aided by such complete decompression. We hope this method of management may prove useful to surgeons faced with the necessity of treating that small group of patients with intestinal obstruction in whom preoperative decompression is not possible.

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A PRIME PHYSIOLOGIC MECHANISM RESPONSIBLE FOR THE FAILURE OF GASTROJEJUNOSTOMY IN THE TREATMENT OF PEPTIC ULCER DISEASE

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INTRODUCTION

GASTROJEJUNOSTOMY was first used in the treatment of peptic ulcer disease in 1881 by Wölfler.[33] Since that time and until 1940, gastrojejunostomy with a variety of modifications was widely and enthusiastically utilized in the treatment of peptic ulcer disease.[2, 3, 14, 15, 17, 22, 23, 30] Gastrojejunostomy was so thoroughly accepted by the Mayos at their clinic that approximately 70 per cent of their patients who had surgical treatment for duodenal ulcer from 1928 through 1935 received the procedure, and it remained their procedure of choice until 1940.[18]

Since 1940, however, the use of gastrojejunostomy in the treatment of peptic ulcer disease has gradually fallen into disrepute because of the increasing number of reports indicating a high incidence of recurrent peptic ulceration.[1, 11, 12, 18, 21]

Experimentally and clinically it has been definitely established that gastroenterostomy in general will produce a marked increase in gastric acid secretion, thus potentiating the very condition the operation was supposedly designed to treat and cure.[8, 9, 16, 19, 25-28, 31]

Early in the investigation of the reason for this increase in gastric acid stimulation, the position of the gastrojejunostomy stoma upon the stomach was first implicated and considered of some importance.[34] It has been recently demonstrated experimentally that the position of the gastrojejunostomy stoma is of relatively little significance and that it is the stoma size which is significantly and directly related to the degree of stimulation of gastric acid secretion.[27]

The antrum of the stomach has also been suggested as a factor influencing the increase in gastric acid secretion. It has been shown experimentally that

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a variety of factors including food, mechanical distention, mechanical irritation, and alkaline reflux can stimulate the antrum and by this manner potentiate the gastric phase of gastric secretion.[4, 6, 13, 20]

Thus a variety of mechanisms responsible for the increase in gastric acid secretion following gastrojejunostomy have been postulated. These suggested possibilities include: (1) repetitive mechanical irritation of the antrum by the "circus" movement of food which, having passed out of the stomach into the duodenum, re-entered the stomach by the afferent jejunal loop, (2) reflux alkaline duodenal juices from the jejunum into the stomach, (3) loss of duodenal inhibition, and (4) increase in the intestinal phase of gastric secretion.

These postulates have been generally accepted and theoretically explain the high recurrence of ulceration seen when gastrojejunostomy is used clinically. The proof for these theories, however, is lacking. This experimental project was designed either to establish or disprove antral hyperstimulation as a factor and to evaluate its significance.

METHOD

A group of 3 mongrel dogs of both sexes, weighing between 10 and 18 Kg., were used. Environmental conditions were carefully controlled as to kennel temperature, time of feeding, and time of collection of Heidenhain pouch secretions.

The results are expressed in milliequivalents of hydrochloric acid secreted for 24 hours and represent an average of 30 days' collections. The results are also expressed in percentage change in acid secretion.

The initial operative procedure consisted of the formation of a typical Heidenhain pouch.

Adequate time was allowed for the animal to recover from the operation before Heidenhain pouch secretions were collected. After 30 consecutive 24-hour Heidenhain pouch collections had been made, the animals were reoperated upon. This operation consisted of a complete submucosal dissection of the antral mucosa from the pylorus to 1 cm. proximal to the incisura angularis and was designed to interrupt any and all nerve elements present in the submucosa. This procedure is called antroneurolysis and is described elsewhere.[6] By previous evidence, this procedure has been found significantly to defunctionalize the antrum. Adequate time was allowed for the animals to recover from the operative procedure before pouch secretions were collected. After 30 consecutive 24-hour pouch collections had been made, the animals were reoperated upon. This operation consisted of a routine anticolic-isoperistaltic low gastrojejunostomy with a stoma size of at least 4 cm. as measured at operation. Postoperatively upper gastrointestinal barium x-ray series revealed a functioning gastrojejunostomy with little or no barium seen passing through the duodenum (Fig. 1). Again the animals were allowed to recover an adequate period of time before Heidenhain pouch collections were resumed, and a final 30-day collection period was made.

RESULTS

The 3 animals tolerated the operative procedures well without evidence of antral necrosis, perforation, or hemorrhage. Results of individual experiments are shown in Fig. 2.

Following antroneurolysis, the average free hydrochloric acid secretion from the Heidenhain pouches decreased from 22.1 to 11.6 mEq. per 24 hours, a decrease of 47.5 per cent.

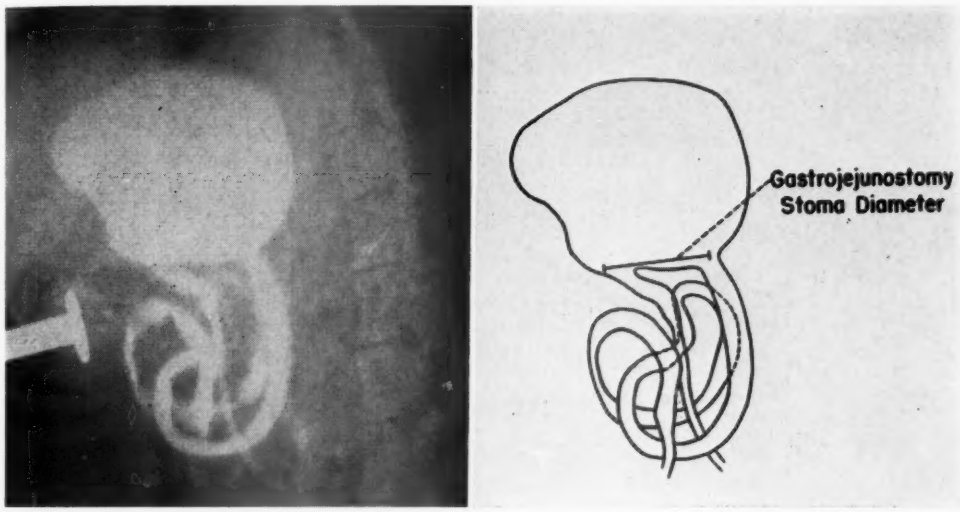

Fig. 1.—Reproduction of a representative x-ray film from an upper gastrointestinal series on one of the animals in this experiment with a 4 cm. gastrojejunostomy stoma. There is no barium passing through the duodenum. All of the barium is being emptied from the stomach by the large stoma gastrojejunostomy. Note the stoma size and primary filling of both jejunal loops.

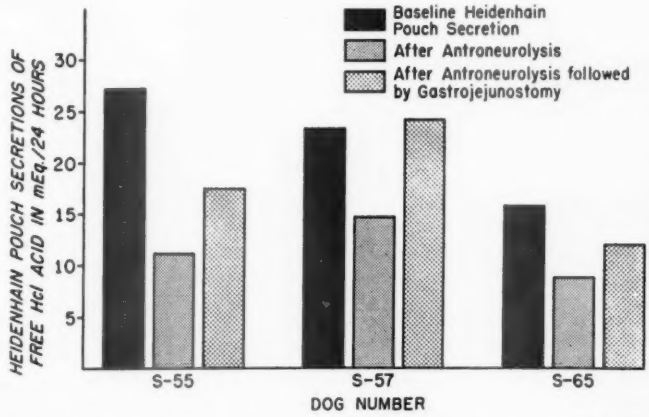

Fig. 2.—Individual Heidenhain pouch free HCl acid values for each of the phases of the experiment. The averages for each phase are: Heidenhain pouch base line 22.1 mEq. per 24 hours; after antroneurolysis, 11.6 mEq. per 24 hours (a 47.5 per cent reduction); after gastrojejunostomy, 17.9 mEq. per 24 hours (a 28.5 per cent increase but still 19.0 per cent below the base line level).

Following gastrojejunostomy, there was a slight increase of free hydrochloric acid (6.3 mEq. per 24 hours), a 28.5 per cent increase. However, this was still 19.0 per cent lower than the previous Heidenhain pouch base line level (Fig. 3).

DISCUSSION

These data again emphasize the marked interruption of antral function produced by antroneurolysis. In these animals with "defunctionalized" antrums a large stoma gastrojejunostomy has no significant effect upon Heidenhain pouch secretions. When we compare these data with results obtained in our laboratory after gastrojejunostomy alone, a difference of 192.0 per cent is noted (Fig. 4). The only difference in the above 2 experimental preparations was a "defunctionalized" antrum in the former. With this in mind, one can conclude that the intact antrum is *primarily* responsible for the marked increase in gastric acid secretion seen after gastrojejunostomy.

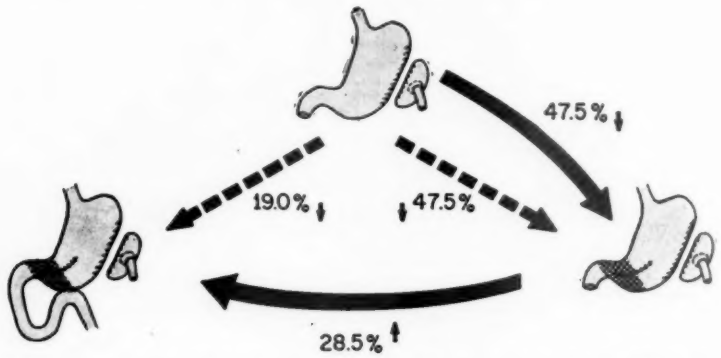

Fig. 3.—Sequence of operative steps and percentage change in Heidenhain pouch secretions. The solid large arrows indicate the sequence of operative steps and the percentage change in pouch secretions between each. The dotted arrows indicate the percentage change in pouch secretions of each step in comparison to the base line level.

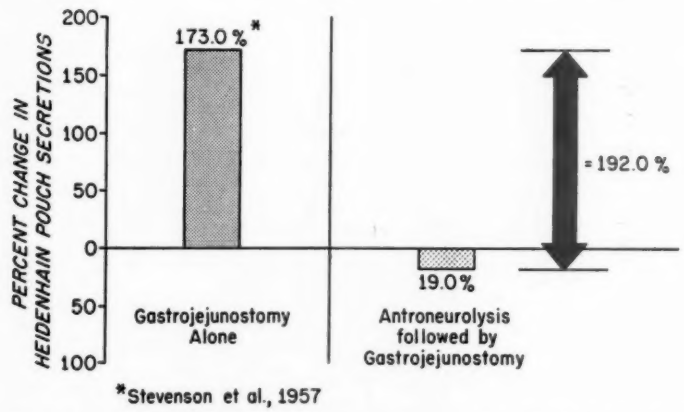

Fig. 4.—Comparison of the percentage change in Heidenhain pouch secretions after gastrojejunostomy alone with and without antroneurolysis. There is a 173.5 per cent increase in acid secretions with gastrojejunostomy alone. When performed after antroneurolysis, there was a 19.0 per cent decrease below the base line value, a difference of 192.0 per cent.

The slight increase in gastric acid secretion seen after antroneurolysis and gastrojejunostomy may be due to a combination of the following: (1) loss of duodenal inhibition, (2) potentiation of the intestinal phase of gastric secretion, and (3) multiple operative procedures alone.[26]

Thus it might be said that the overstimulation of the antrum is an exceedingly significant factor responsible for the ulcerogenic potentialities of gastrojejunostomy.

SUMMARY

Gastrojejunostomy produces no significant increase in Heidenhain pouch secretions in animals with "defunctionalized" antrums. Thus, overstimulation of the antrum is a prime explanation why gastrojejunostomy alone is an ulcerogenic procedure, and by itself should be avoided in the treatment of peptic ulcer disease.

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SOME OBSERVATIONS ON THE MECHANISM OF POSTOPERATIVE TRANSIENT ALDOSTERONISM WITH SPECIAL REFERENCE TO EARLY CHANGES IN SERUM ELECTROLYTE LEVELS

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THERE is convincing evidence that aldosterone plays an important role in the retention of sodium (Na^+) and increased excretion of potassium (K^+) which follow surgical trauma. In previous work[11, 13] it was found that there is increased aldosterone activity in the urine of patients after operation and a significant correlation[10, 15] between the excretion level of aldosterone and the logarithm of the Na^+/K^+ ratio in the patient's urine before and after operation, and by the time the Na^+/K^+ ratio returns to its preoperative level the aldosterone level has also returned to its preoperative level.[10, 15] It was suggested that this metabolic phenomenon be called postoperative transient aldosteronism.[10] Subsequently, aldosterone has been identified chemically in postoperative urine.[14, 20]

Many of these findings have now been confirmed by other workers[21, 22] but the mechanism responsible for postoperative aldosteronism has not been elucidated. There is, however, a good deal of evidence that aldosterone secretion is not under the direct control of the pituitary[7, 9]; and it has been reported that normal subjects fed diets rich in potassium show increased aldosterone excretion,[3, 16] and that the amount of aldosterone secreted by the perfused adrenal gland in vitro can be altered by altering, though admittedly somewhat drastically, the Na^+/K^+ ratio of the perfusion fluid.[19] It appeared conceivable, therefore, that after surgical operations increased serum K^+, resulting from absorption of K^+ from injured tissue in the field of operation, might stimulate the adrenals to secrete more aldosterone and that this increased secretion might continue for some time after the stimulus had ceased to operate. The present investigation was undertaken to test this hypothesis.

METHODS

Plan of Investigation.—The patients studied comprised adults of both sexes who were subjected to operations of various degrees of severity and who showed no evidence of electrolyte imbalance or adrenocortical disturbance prior to operation. As a general rule patients requiring intravenous infusion of

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fluid during the first 24 hours after operation have been excluded, but an exception has been made in one case (No. 15) in which the findings appear to be of special interest.

As a preliminary, blood samples were obtained from a small group of patients before and after operation for determinations of serum K^+ and Na^+, but no urine was collected. The preoperative samples were obtained on the day before operation (between 2 and 4 P.M.) and immediately before starting the anesthetic (about 8 A.M.). The postoperative samples were taken 4, 8, 12, and 24 hours after making the skin incision.

It was found that the serum K^+ was usually increased in the 8-hour specimen but not in the 4-hour specimen. In the light of this observation a definitive plan of investigation was decided upon and was used in all subsequent patients. Preoperative blood samples were obtained at the same times as before. Postoperative blood samples were obtained 6, 12, and 24 hours after operation. As each sample was taken the bladder was emptied by means of an indwelling catheter inserted at the end of the operation, and the urine was collected for aldosterone assay. In addition, preoperative collections of urine were made. Generally speaking this procedure proved very satisfactory, but occasionally the 6-hour urine specimen could not be collected because the patient withdrew the catheter while reviving from the anesthetic.

Estimations of K^+ and Na^+ in Serum.—Blood was collected from an elbow or forearm vein in a siliconed syringe without any anticoagulant and centrifuged immediately in a siliconed tube for 10 minutes. The serum was separated from the cells immediately after centrifugation to avoid errors due to diffusion of K^+ from the red cells, which can occur without hemolysis.[1] The estimations of K^+ and Na^+ were made with an EEL flame photometer following the procedure described elsewhere.[1]

Great care was taken to avoid hemolysis, but in spite of this some specimens became hemolyzed, principally because the patients tended to be somewhat uncooperative when the postoperative samples were being obtained. Except in 2 instances where the presence of some degree of hemolysis clearly does not affect the conclusions drawn, all patients whose blood samples showed hemolysis have been excluded from the results.

Bioassay for Aldosterone Activity.—The method described in previous papers[8, 12] has been modified in 2 respects: (1) the urine was acidified to pH 1, extracted with chloroform 40 minutes after acidification, and re-extracted after 24 hours; and (2) an aliquot of the extract equivalent to a 20-minute output of urine was injected to each adrenalectomized rat in the bioassay, instead of a 3-hour equivalent which had been used in earlier work.

When specimens of urine could not be dealt with immediately they were stored at –20° C. in a Deepfreeze.

As before, the aldosterone activity of each human urine sample has been determined by finding the value of $\frac{100.\ R_T}{R_C}$ where R_T is the mean ratio of Na^+/K^+ in the urine of adrenalectomized rats injected with an aliquot of the

material extracted from the sample, and R_C is the corresponding value in a control group of adrenalectomized rats. A fall in the value of $\frac{R_T}{R_C}$ indicates increased aldosterone activity, and vice versa.

RESULTS

Serum K^+ and Na^+ Levels After Operation.—In all the patients' studies the serum K^+ rose after operation (Tables I and II). In the first group of patients, whose blood samples were collected 4, 8, 12 and 24 hours after operation (Table I), the maximal rise was usually observed in the 8-hour sample, and in the second group of patients whose samples were collected 6, 12, and 24 hours after operation the maximal rise was observed in either the 6- or the 12-hour sample. The 2 preoperative values for the serum K^+ usually differed, and in Table III the maximal rise has been calculated in 2 ways: first, in relation to the immediate preoperative value, and, second, in relation to the higher of the 2 preoperative values. A rise of 0.50 mEq. per liter or more above the higher of the 2 preoperative values has been designated, somewhat arbitrarily, a large rise.

Twenty-four hours after the beginning of the operation all patients except one showed a fall in the serum K^+ level (Table III) similar in magnitude to the maximal rise observed previously.

Sodium levels showed a slight tendency to diminish in the 12-hour samples and a clear-cut diminution in the 24-hour samples (Tables I and II).

The magnitude of the postoperative K^+ rise varied considerably from one patient to another. Operations in which there was a good deal of laceration of muscle, such as radical mastectomy (Cases 6 and 15) and lumbar sympathectomy (Case 16), seemed to cause a relatively large rise, but a large rise also occurred in 3 out of 4 patients following thyroidectomy. Only a slight rise was observed in the patient (Case 12) subjected to amputation through the thigh, but absorption from the site of operation may well have been limited because the patient was suffering from obliterative arterial disease.

It might be suggested that the postoperative rise in serum K^+ was not due to the operation but was dependent simply upon a normal diurnal variation in the serum K^+ level. Recent observations,[5] however, do not support the view that there is any regular rhythm of this kind; moreover, if there were, one would expect the values for the samples obtained 4 to 6 hours after operation to be about the same as the values for the first preoperative samples which were obtained approximately 24 hours earlier, whereas there is in fact a consistent difference. The possibility that the elevation in serum K^+ was due to hemoconcentration can also be eliminated in view of the fact that the Na^+ level remained almost unchanged during the period of maximal K^+ rise.

Excretion of Aldosterone at 6-Hour Intervals After Operation.—The results are summarized in Table IV. We have not attempted to convert the figures expressing the results of the bioassay into μg of aldosterone because the method of bioassay is not sufficiently accurate,[2] nor have we compared the values for aldosterone activity reported here with those reported in previous

TABLE I. SERUM ELECTROLYTE VALUES (MEQ./L.) BEFORE AND AFTER OPERATION

NUMBER AND SEX OF PATIENT	VALUES BEFORE OPERATION				VALUES AFTER OPERATION							
	DAY BEFORE		IMMEDIATELY BEFORE		AT 4 HOURS		AT 8 HOURS		AT 12 HOURS		AT 24 HOURS	
	K^+	NA^+	K^+	NA^+	K^+	NA^+	K^+	NA^+	K^+	NA^+	K^+	NA^+
1 F	3.65	136.0	3.85	133.0	4.1	135.0	4.75	135.0	—*	—*	4.6	123.0
5 F	4.1	141.0	3.9	139.0	—*	—	4.3	136.5	4.2	136.5	4.0	136.5
6 F	3.5	140.0	4.3†	140.0	—*	—	4.8	144.0	4.1	140.0	4.1	139.0
7 F	—*	—	3.8	141.0	4.1	144.0	4.1	144.0	3.9	141.0	3.8	136.5
8 F	4.2	145.0	3.95	145.0	4.1	145.0	4.65	146.0	4.7	145.0	—*	—
10 F	3.9	146.0	4.2	137.0	3.95	140.0	4.8	137.0	4.6	136.0	4.0	134.0
Mean±S.E.	3.87±0.13	141.60±1.81	4.00±0.08	139.17±1.61	4.06±0.09	141.00±2.27	4.57±0.09	140.42±1.89	4.30±0.15	139.70±1.64	4.10±0.13	133.80±2.81

*Sample not obtained.
†Some hemolysis.

TABLE II. SERUM ELECTROLYTE VALUES (MEQ./L.) BEFORE AND AFTER OPERATION

NUMBER AND SEX OF PATIENT	VALUES BEFORE OPERATION				VALUES AFTER OPERATION					
	DAY BEFORE		IMMEDIATELY BEFORE		AT 6 HOURS		AT 12 HOURS		AT 24 HOURS	
	K^+	NA^+	K^+	NA^+	K^+	NA^+	K^+	NA^+	K^+	NA^+
11 M	3.45	141.0	3.15	143.0	3.3	141.0	3.65	139.5	3.45	133.0
12 M	4.0	141.0	3.8	144.5	3.95	139.5	4.15	139.5	3.95	134.0
13 F	4.0	144.0	4.0	141.0	4.1	139.5	4.15	139.5	3.8	135.5
14 F	4.0	141.0	4.0	141.0	4.4	135.5	3.9	136.5	4.0	136.5
15 F	4.15	146.0	3.65	144.0	4.7*	144.0	3.75	143.0	4.15	139.5
16 M	4.0	141.0	4.7†	141.0	5.6	141.0	6.0	139.5	4.1	139.5
19 M	3.9	141.0	4.1	141.0	4.5	141.0	4.3	139.5	4.5	138.0
20 F	4.1	139.5	3.3	138.0	4.4	139.5	—‡	—	4.2	135.5
21 F	3.4	135.5	3.4	136.5	4.2	136.5	4.1	138.0	4.0	138.0
22 F	3.6	141.0	3.6	141.0	4.2	141.0	4.7	141.0	3.5	141.0
Mean ±S.E.	3.86±0.09	141.10±0.86	3.77±0.14	141.10±0.78	4.33±0.18	139.85±0.77	4.30±0.24	139.56±0.45	3.96±0.10	137.05±0.82

*Blood transfusion started after this collection.
†Some hemolysis.
‡Sample unobtainable.

TABLE III. SERUM K+ BEFORE AND AFTER OPERATION
(Analysis of Data in Tables I and II)

NUMBER AND SEX OF PATIENT	OPERATION	DIFFERENCE IN PREOPERATIVE VALUES $K_1 - K_2$* (MEQ./L.)	MAXIMAL RISE (MEQ./L.)			FALL (MEQ./L.)
			TIME OF OCCURRENCE (HOURS AFTER OPERATION)	IN RELATION TO THE VALUE IMMEDIATELY BEFORE OPERATION	IN RELATION TO THE HIGHEST OF THE 2 PREOPERATIVE VALUES	DIFFERENCE BETWEEN MAXIMAL POSTOPERATIVE VALUE AND VALUE 24 HOURS POSTOPERATION
1 F	Gastrectomy	−0.20	8	0.90	0.90	0.15
5 F	Cholecystectomy	0.20	8	0.40	0.20	0.30
6 F	Radical mastectomy	−0.80†	8	0.50‡	0.50‡	0.70
7 F	Cholecystectomy	—	4 & 8	0.30	—	0.30
8 F	Thyroidectomy	0.25	12	0.75	0.50	—
10 F	Thyroidectomy	−0.30	8	0.60	0.60	0.80
11 M	Herniorrhaphy	0.30	12	0.50	0.20	0.20
12 M	Leg amputation	0.20	12	0.35	0.15	0.20
13 F	Cholecystectomy	0.00	12	0.15	0.15	0.35
14 F	Thyroidectomy	0.00	6	0.40	0.40	0.40
15 F	Radical mastectomy	0.50	6	1.05	0.55	0.55
16 M	Lumbar sympathectomy	−0.70†	12	1.30‡	1.30‡	1.90
19 M	Partial colectomy	−0.20	6	0.40	0.40	0.00
20 F	Radical mastectomy	0.80	6	1.10	0.30	0.20
21 F	Laparotomy, section of adhesions	0.00	6	0.80	0.80	0.20
22 F	Thyroidectomy	0.00	12	1.10	1.10	1.20
Mean ± S.E.		+0.0033± 0.1074	—	0.66 ± 0.09	0.54 ± 0.09	0.50 ± 0.13

*K_1 = serum K^+ the day before operation; K_2 = serum K^+ immediately before operation.
†The absolute value of the difference was smaller than the figure tabulated, since the second preoperative sample was slightly hemolyzed.
‡The actual rise was higher than the figure tabulated, since the second preoperative sample was slightly hemolyzed.

papers[10, 11, 13, 15] because the method of extraction and the dose of extract injected into the rats were not the same as those employed previously. It does seem reasonable, however, to compare the values obtained in the same patient, by the same method, before and after operation.

It will be seen that 5 of the 7 patients studied showed increased aldosterone activity during the first 24 hours after operation. The increase occurred at different times in different patients, however, and there did not appear to be any correlation either between the magnitude of the rise in serum K^+ and the extent of the increased aldosterone excretion or between the time of the maximal rise in serum K^+ and the time at which aldosterone excretion was maximal.

DISCUSSION

The results reported above show that there is a temporary and, in most cases, significant rise in the level of serum K^+ within 12 hours after all operations of moderate severity. The K^+ level returns to approximately preoperative levels within 24 hours of operation, by which time another electrolyte alteration is present in serum, namely, a fall in serum Na^+. It seems most likely

TABLE IV. SHOWING ABSENCE OF CORRELATION BETWEEN RISE IN SERUM K^+ AND ALDOSTERONE EXCRETION

NUMBER AND SEX OF PATIENT	OPERATION	MAXIMAL RISE IN SERUM K^+ OVER IMMEDIATE PREOPERATIVE VALUE		ALDOSTERONE EXCRETION		
		HOURS AFTER OPERATION	VALUE (MEQ./L.)	HOURS IN RELATION TO OPERATION*	VALUE†	DEGREE OF POSTOPERATIVE INCREASE
11 M	Herniorraphy	12	0.50	−24 to 0	95.0	----
				0 to 6	85.3	Slight
				6 to 12	100.3	None
				12 to 24	91.8	Minimal
12 M	Amputation of leg	12	0.35	−24 to 0	68.0	----
				0 to 6	99.0	None
				6 to 12	84.2	None
				12 to 24	69.8	None
13 F	Cholecystectomy	12	0.15	−24 to 0	70.0	----
				0 to 6	55.6	Moderate
				6 to 12	66.7	Minimal
				12 to 24	39.1	Large
14 F	Thyroidectomy	6	0.40	−24 to 0	83.1	----
				0 to 6	63.2	Moderate
				6 to 12	115.8	None
				12 to 24	53.2	Large
15 F	Radical mastectomy	6	1.05	−24 to 0	73.0	----
				0 to 6	81.4	None
				6 to 12	75.2	None
				12 to 24	78.6	None
19 M	Partial colectomy	6	0.40	−24 to 0	72.5	----
				0 to 6	95.6	None
				6 to 12	48.5	Large
				12 to 24	65.9	Slight
21 F	Laparotomy and division of adhesions	6	0.80	−24 to 0	79.3	----
				0 to 6	47.4	Large
				6 to 12	95.7	None
				12 to 24	92.3	None

*Although the duration of the urine collection was different in the first and fourth intervals, the results are comparable, because in all determinations only an aliquot equivalent to a 20-minute output of patient's urine was injected to each rat used in the bioassay.

†Lower values indicate more activity (see Methods).

that at least part of the elevated serum K^+ has been contributed by K^+ absorption from the operative field. These findings confirm and extend those of Howard.[6]

From work done in this laboratory[10, 11, 13, 14, 15, 20] and elsewhere,[21, 22] it has become clear that a postoperative state of aldosteronism is a common feature of what Moore[17] has called the normal pattern of the metabolic response to surgery, and in the present investigation most of the patients whose aldosterone activity in urine was studied showed an increased level in one or other of the 6-hour samples. The fact that 2 patients failed to show this response does not invalidate the general conclusion because the highest increase of aldosterone excretion may occur on the second day,[15] or even later,[21] after operation. Moreover, Patient 15 required a blood transfusion 6 hours after the operation and this, for reasons considered later, may have inhibited aldosterone secretion.

The findings suggest, however, that there is no correlation between the magnitude and time relations of the rise in serum K^+ after surgical operations

and the excretion of aldosterone and therefore do not support the hypothesis we set out to test. It could of course be argued that there might be a correlation between the serum K^+ rise and the blood levels of aldosterone, which we have not attempted to estimate, but this seems very unlikely in view of the experiments of Farrell and his colleagues,[4] published while the present investigation was in progress, in which it was found that there was no correlation between the serum K^+ and the aldosterone level of venous adrenal blood in dogs subjected to trauma.

If postoperative aldosteronism cannot be attributed to stimulation of the adrenal either by the pituitary or by changes in serum electrolyte levels, can any other explanation be suggested? A hint has, it would seem, been provided by recent work of Rauschkolb and Farrell,[18] which suggests that aldosterone secretion is regulated by a circulating tropic hormone elaborated by a center in the diencephalon in response to a fall in intracranial blood pressure or blood flow. If, as seems likely, this center is damaged or its function is disturbed, during the operation of hypophysectomy, it would be easy to understand why, as one of us[7, 9] has recently shown, there is no sharp increase in aldosterone excretion after this particular operation, despite the fact that the hypophysectomized patient is not deprived of the capacity to secrete basal amounts of aldosterone.

The fact that Patient 15, who received a blood transfusion beginning 6 hours after operation, failed to show any postoperative increase in aldosterone excretion, though an isolated observation, also accords well with the hypothesis of a diencephalic center sensitive to changes in intracranial blood pressure or flow as the regulator of aldosterone production after surgical trauma.

SUMMARY

After surgical operations of moderate severity there is a rise in the level of serum K^+ which reaches a maximum between 6 and 12 hours after operation. Twenty-four hours after operation the patients show a fall in serum K^+ of a similar magnitude to the maximal rise observed previously.

There is also a postoperative rise in the urinary excretion of aldosterone, but the time at which this occurs varies greatly, and the extent of the rise shows no correlation with either the magnitude or the time relations of the serum electrolyte changes.

It is concluded that the postoperative rise in serum K^+ is not the stimulus to postoperative transient aldosteronism. Instead, it is suggested that the findings are consistent with the hypothesis that a circulating tropic hormone, elaborated by the diencephalon in response to a diminution in intracranial blood pressure or blood flow, is the stimulus to postoperative aldosteronism.

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AIR CONTRAST CHOLANGIOGRAPHY

A Preliminary Report

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THE problem of overlooking calculi in the extrahepatic biliary tract has been partly solved by the addition of operative cholangiography to the surgical armamentarium. However, even this procedure as it is currently performed has its limitations. The likelihood of not visualizing stones present in markedly dilated ducts owing to the density of the dye remains a problem in the occasional patient. Similarly the presence of very small stones in ducts of normal size creates the same hazard as demonstrated experimentally by Ashmore.[1]

Since air contrast techniques are being introduced successfully in the roentgenologic examination of other regions of the body (that is, bronchial tree, kidney, and so forth), the method may be applicable in the extrahepatic biliary system in an effort to demonstrate small calculi which might otherwise be unrecognized.

Current investigations are now proceeding at our institution following successful pilot experiments in the laboratory.

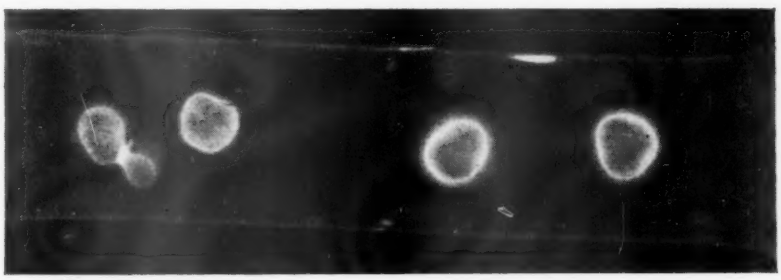

Fig. 1.—Biliary calculi in rubber tubing following removal of Diodrast and replacing with air.

LABORATORY STUDY

Our present technique of air contrast cholangiography for use at the operating table has evolved from two experimental studies. Biliary calculi were placed in thin rubber tubes which were ligated at each end. A contrast medium (70 per cent Diodrast) was then injected into the tubes in order to coat the calculi. The dye was then withdrawn and air was injected. X-rays were obtained before and after instillation of air and it was our feeling that better visualization of the stones was obtained with the air contrast (Fig. 1).

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Fig. 2.—Postoperative air contrast cholangiogram obtained through indwelling common duct T tube.

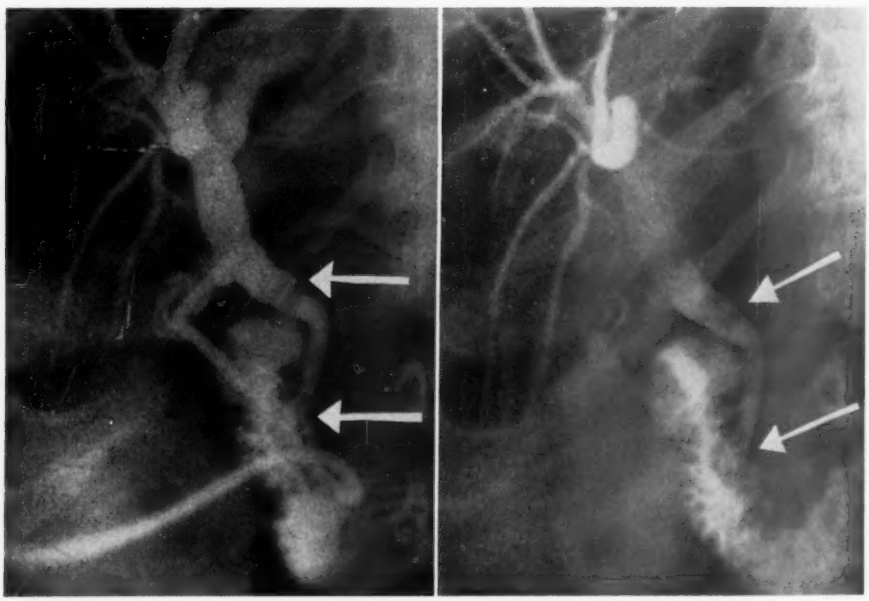

Fig 3. Fig. 4.

Fig. 3.—Routine operative cholangiogram demonstrating the presence of common duct stones *(arrows)*.

Fig. 4.—Air contrast cholangiogram in the patient shown in Fig. 3 with improved definition of calculi.

Further studies were made using dogs with common ducts dilated by ligation of the duct at a previous operation. Biliary calculi (human) of varying sizes were placed in the ducts and routine cholangiograms and air contrast studies were carried out. Results of these experiments were encouraging. The introduction of air into the biliary tree had no apparent untoward effect on the animals.

Studies were then undertaken in patients who had undergone previous common duct exploration and in whom a T tube was in place during the postoperative period. The postoperative air contrast cholangiograms were obtained in the following manner. The patient was positioned satisfactorily on the x-ray table and a scout film obtained. Diodrast (35 per cent) was then injected into the T tube in increments of 10 c.c., with a film being taken after each increment. Three films were taken using a total of 30 c.c. of dye. Immediately after the last 10 c.c. of dye was injected, 30 to 50 c.c. of air was injected and a film obtained instantly (Fig. 2).

A total of 17 patients have been examined.

This technique has now been transferred to the operating room and at present a series of patients is being compiled who have had air contrast cholangiography by the above described technique (Figs. 3 and 4).

DISCUSSION

The method of air contrast cholangiograms described appears to be feasible. Air bubbles have not posed a problem nor has the introduction of air interfered with obtaining additional pictures using dye. That the procedure appears to be safe is borne out by the study conducted in postoperative patients. In 17 patients there have been no ill effects, and only slight discomfort in the right upper quadrant of the abdomen has been experienced by a few patients. Various improvements in the technique are being explored by using different concentrations of radiopaque material, using dye in conjunction with wetting agents, and reducing the escape of air into the duodenum by agents producing spasm of the sphincter of Oddi.

It is anticipated that air contrast cholangiography will prove to be of assistance in detection of calculi particularly in patients with markedly dilated ducts.

SUMMARY

1. Air contrast cholangiography, an adjunct to operation cholangiography, has been described.

2. The method appears to be feasible, safe, and useful.

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THE EFFECT OF CHRONIC PANCREATITIS ON PRESSURE TOLERANCE IN THE HUMAN PANCREATIC DUCT

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OBSERVATIONS on the range of pressures encountered in the pancreatic ductal system of experimental animals have been recorded on numerous occasions.[2, 8, 10, 11] However, we have not encountered a study of pressures in the human pancreatic ductal system that did not involve cannulization of the pancreatic duct through the sphincter of Oddi, frequently following its severance for therapeutic purposes.

My description[3] and later the reports by Ellison,[7] Longmire,[9] Aird,[1] and others of retrograde pancreaticojejunostomy in cases of chronic pancreatitis have provided a method for the direct mensuration of pancreatic duct pressures in the human in which the terminus of the pancreatic and common bile ducts has remained undisturbed.

The rationale and technique of the operative procedure have been described elsewhere.[4] The occasional difficulty encountered in suturing the pancreatic duct to the jejunal mucosa led to the use, in appropriate cases, of a splinting catheter which was removed as the anastomosis was completed. In several instances it was deemed advisable to leave the splint in situ to increase the possibility of achieving a patent internal pancreatic fistula. This was accomplished by threading the catheter through the lumen of the Roux-Y limb of jejunum and permitting it to emerge to the outside via a purse-string enterostomy and abdominal wall stab wound. By use of a fine caliber Foley catheter splint in the distal pancreatic ductal system, manometer pressures were recorded. (Fig. 1.)

It is generally agreed that resting pressures in the pancreatic duct of the dog do not exceed 15 to 20 cm. H_2O. With this reference point, the following study was performed.

MATERIALS AND METHODS

Four patients with cutaneous pancreatic fistula served as controls (3 from penetrating wounds and one following resection of the tail of the pancreas and stomach for carcinoma). Nine patients with severe chronic pancreatitis were studied within 4 days of pancreaticojejunostomy.

In both groups a Foley catheter (size 8 French) was passed through the fistula. The 3 c.c. balloon was inflated and the catheter connected to a 10 c.c.

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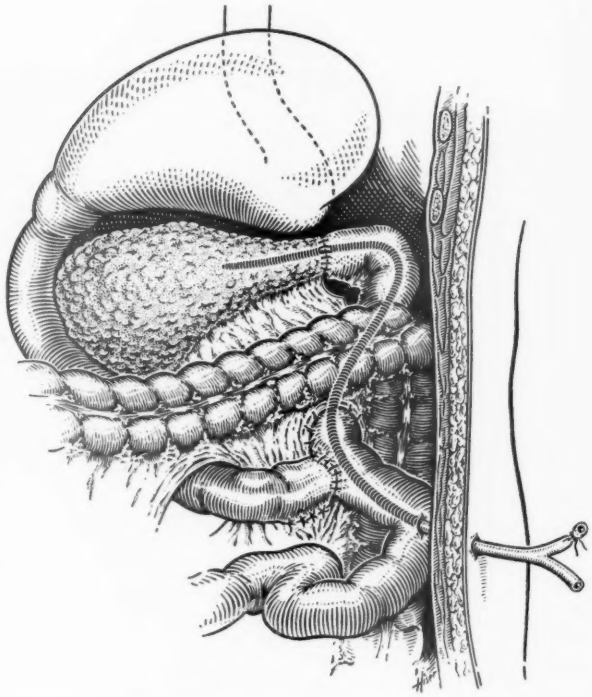

Fig. 1.—Semidiagrammatic representation of the completed pancreaticojejunostomy. Note the method of cannulation of the pancreatic duct using a small Foley catheter.

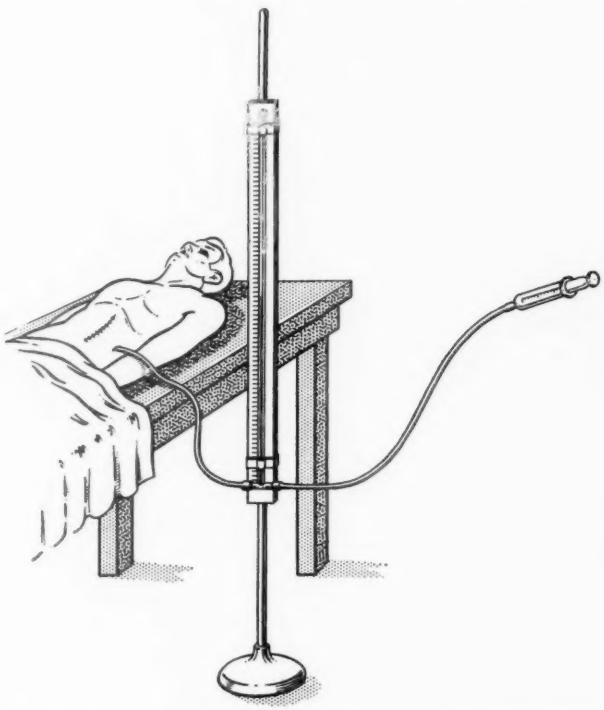

Fig. 2.—Illustration of the method used to study the tolerance of the pancreatic ductal system to pressure loads.

syringe through a manometer (Fig. 2). Breakfast and medication were omitted on the morning of study. With the patient in the supine position, the zero level of pressure was set at 40 per cent of the distance from the surface of the examining table to the skin of the abdomen. Any error introduced in selecting this zero level was thus common to both the control and the study groups.

The closed system was then gradually filled with isotonic saline at room temperature to zero pressure. Perfusion pressure was then increased at the rate of 0.5 cm. per second. The level of pressure at which there was a sudden fall was defined as the tolerance pressure. Fluoroscopic examination with Diodrast instead of saline confirmed the tolerance pressure as occurring simultaneously with decompression into the duodenum. Three separate observations were made on each patient. Three additional observations were made after increasing the rate of perfusion to 1.0 cm. per second.

RESULTS

Table I summarizes the observed data on resting and tolerance pressures. Resting pressure in the control group ranged from 9 to 13 cm. H_2O with an average of 10.3 cm. Tolerance to pressure increments of 0.5 cm. H_2O per second was observed up to 17 cm. (range 15 to 22 cm.) and to 19 cm. by increasing the rate of perfusion pressure to 1.0 cm. per second. Whether or not the increased tolerance to more rapid increment in pressure is of significance is not known, but we suspect it may be related to the lag in transmission of pancreatic duct pressure to the manometer at the more rapid rate.

TABLE I. SUMMARY OF OBSERVATIONS OF RESTING AND TOLERANCE PRESSURES

	RESTING PRESSURE		TOLERANCE (0.5 CM./SEC.)		TOLERANCE (1.0 CM./SEC.)	
	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN
Controls	9-13*	10.3	15-22	17.6	16-25	19.4
Chronic pancreatitis	16-37	28.3	29-57	41.2	31-61	43.8

*Denotes centimeters of water.

Resting pancreatic duct pressure among the group of patients with chronic pancreatitis averaged 28 cm. H_2O (range 16 to 37 cm.). Tolerance to pressure increments of 0.5 cm. per second appeared at about 41 cm. and at 44 cm. with 1.0 cm. per second pressure increases.

DISCUSSION

The data suggest that in patients with chronic pancreatitis intraductal pressure must rise to over twice the normal values before there is decompression into the duodenum. This implies an increased impedance to the outflow of external pancreatic secretions in the scarred and fibrotic pancreas. Whether or not this partially obstructing mechanism is of importance in the etiology of pancreatitis is not known; but it apparently becomes important in the later stages of the disease.

It should be stressed that the studies reported here are acute and represent only the tolerance of the pancreatic ductal system to increased ductal

pressures. They do not necessarily relate to changes in pancreatic secretory pressures that may accompany inflammatory disease. Studies in this direction are now being carried out.

The findings do suggest, however, that an effort to detect the presence of a partially obstructed pancreatic duct will yield a group of patients in whom surgical decompression of the obstructed duct may be beneficial. A separate report is being made[6] dealing with this aspect of the problem.

SUMMARY AND CONCLUSIONS

1. Pancreatic intraductal resting pressures have been measured in 4 patients without pancreatic inflammatory disease and in 9 patients with chronic pancreatitis.

2. The findings suggest that in patients with chronic pancreatitis pancreatic duct pressure must at least double before evacuation into the duodenum.

3. It is suggested that detection of pancreatic duct obstruction, when present in pancreatitis, may yield a group of patients who will benefit from operative decompression.

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HEREDITARY OCCURRENCE OF BRANCHIAL CLEFT FISTULAS

Report of an Interesting Family

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RECENTLY at the Mayo Clinic 2 patients from the same family were operated upon for branchial fistulas. A third member of this family had been operated upon in 1929 and 1935. This is a report of these cases and of the family tree. The familial tendency for branchial fistulas has been noted by several authors.[1, 2, 4-7] In a recent publication one author[3] has stated that these conditions are developmental rather than genetic in origin, but this observation has not been validated either in the literature or by our observations.

CASE REPORTS

Case 1.—A white woman, 58 years of age, came to the Mayo Clinic on Sept. 24, 1941, with a chief complaint of drainage in her throat for one year. Six years prior to admission she had noticed a swelling in her throat which she believed to be a goiter. One year before admission it had been observed that pressure over the swelling in the right side of the neck caused purulent material to drain into the throat, behind the right tonsil. Family history disclosed that her daughter had been operated upon for bilateral branchial cysts at the Mayo Clinic.

Physical examination revealed a well-developed, well-nourished woman with a soft palpable mass to the right of the trachea. Pressure on this mass caused purulent drainage into the throat behind the right tonsil. A small sinus was seen on the left side of the neck. The results of laboratory examinations were normal.

On Sept. 27, 1941, Dr. S. W. Harrington removed, through a transverse incision, a cyst from the right branchial cleft and also an infected sinus tract. He noted that the sinus tract began as a blind cord in the mediastinum, extended upward and backward into the neck, and passed along the carotid arteries and beneath the posterior belly of the digastric muscle to the posterior tonsillar fossa. The upper portion of the sinus tract was ligated at the tonsillar fossa.

The pathologist reported a branchial cleft cyst measuring 7.6 by 1.9 cm. lined by columnar mucus-secreting cells with lymphoid tissue in the wall.

The patient returned to the Mayo Clinic on Aug. 7, 1957, at the age of 73 years, accompanied by her grandson. She was asymptomatic but had a fistula in one of the left branchial clefts. Results of physical and laboratory examinations were otherwise normal. On Aug. 10, 1957, one of us (O. H. B.) excised the left branchial cleft fistula through 2 transverse stepladder incisions. The fistulous tract was cystic in the lower half. It was traced upward along the anterior border of the sternocleidomastoid muscle to a point at which it extended deep between the external and internal carotid arteries, over the hypoglossal nerve, and beneath the posterior belly of the digastric muscle. The tract was ligated 2 to 3 mm. from the internal opening.

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The pathologist reported a left branchial cleft sinus measuring 4 by 2 by 2 cm. lined partially by squamous and partially by ciliated columnar epithelium (Fig. 1).

The patient's convalescence was uneventful and she was dismissed on the fifth postoperative day.

CASE 2.—On June 18, 1929, a 13-year-old white girl (daughter of the patient in Case 1) came to the Mayo Clinic with the chief complaint of bilateral sinuses in the neck, which had been present since birth. The sinuses had begun to discharge purulent material intermittently when she was 3 years old, and the fistula on the left had been infected on several occasions. At this time it was noted from the history given that 10 members of the maternal side of her family had sinuses in the neck.

Physical examination revealed bilateral branchial cleft fistulas. The fistula on the right was raised and somewhat tender, and pus could be expressed from each fistula. Physical and laboratory examinations were otherwise noncontributory.

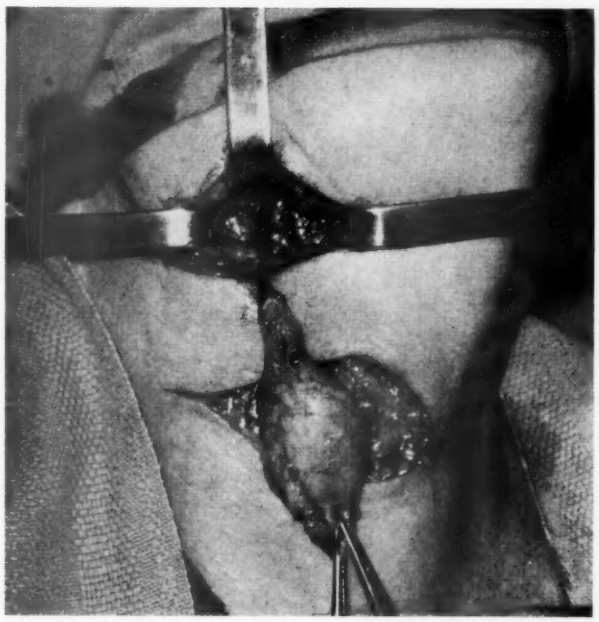

Fig. 1.—Branchial cleft fistula with cystic dilatation of lower part of tract just before excision (Case 1).

On June 26, 1929, Dr. Harrington excised the left branchial cleft fistula. Methylene blue was injected into the cutaneous opening of the left fistula and dye came into the mouth posterior to the left tonsil. The tract extended along the carotid arteries and under the digastric muscle. It was ligated close to the tonsillar fossa. The right fistula was not excised at this time.

The patient returned June 17, 1935, because the right fistula had begun to drain yellow, watery material. Physical examination revealed a small fistulous opening on the right side of the neck 1 cm. anterior to the sternocleidomastoid muscle, at the level of the thyroid cartilage, and swelling under the right mandible in the submaxillary region. Results of physical examination were otherwise normal.

Iodized oil was injected into the sinus, and the internal opening was demonstrated by the escape of purulent material. This opening was on the anterior lip of the right posterior tonsillar pillar. A roentgenogram of the neck showed a pocket filled with contrast media opposite the second, third, and fourth cervical vertebrae.

On June 21, 1935, Dr. Harrington excised the right branchial fistula. The sinus passed between the internal and external carotid arteries, underneath the posterior belly of the

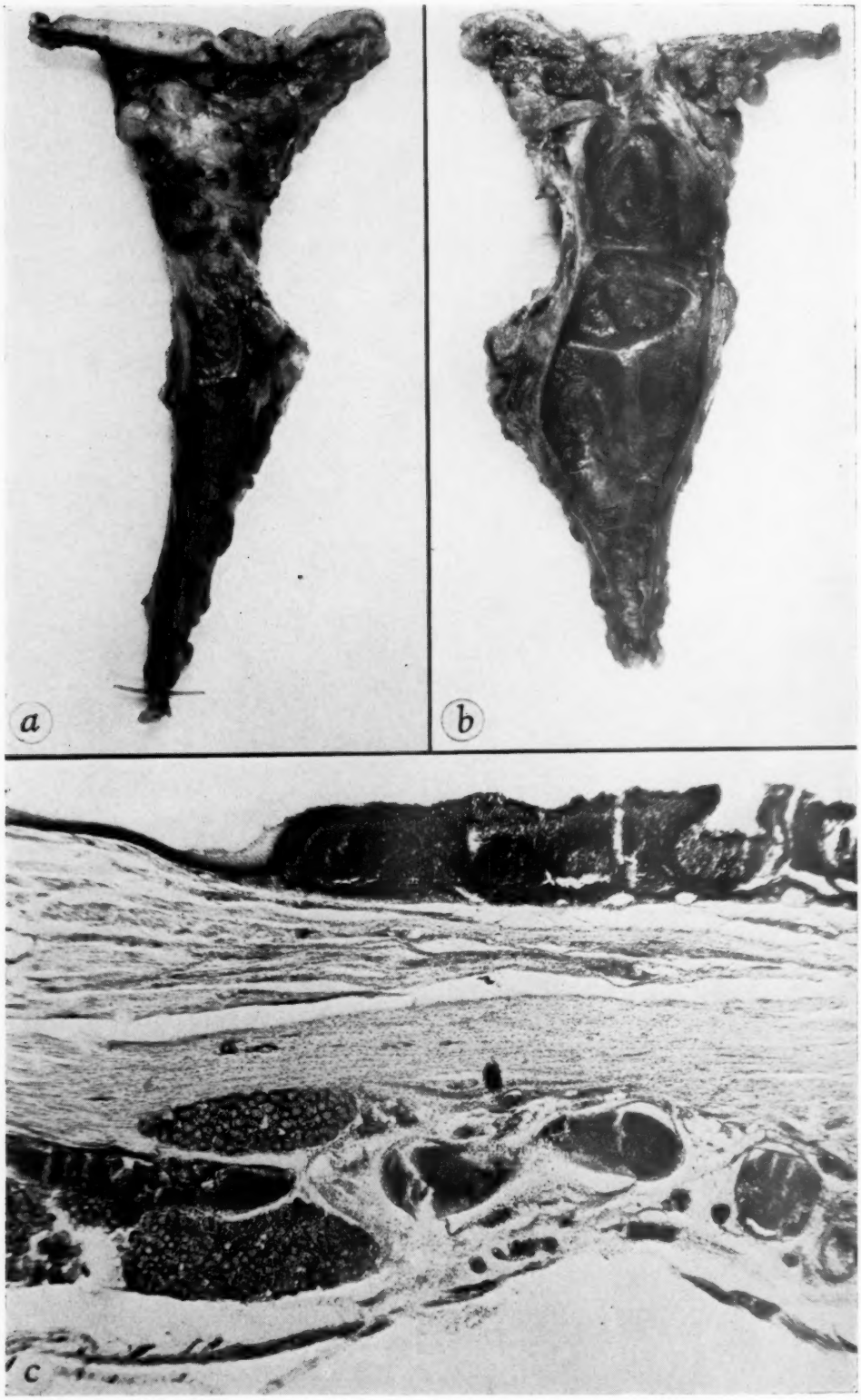

Fig. 2.—Branchial cleft fistula (Case 2). *A*, Intact specimen. *B*, Fistula opened. *C*, Microscopic section showing squamous epithelial lining (hematoxylin and eosin, ×27).

digastric muscle, and under the stylohyoid muscle, and terminated at the posterior tonsillar fossa. The pathologist reported a conical cyst 8 cm. long, 4 cm. wide at the base, and 1 cm. at the apex (Fig. 2, *A* and *B*), lined by squamous epithelium (Fig. 2, *C*).

When the patient returned on Aug. 10, 1957, with her mother and her son (the patient of Case 3), she was not having any further difficulty. She planned to bring another child in the near future for excision of bilateral branchial fistulas.

CASE 3.—The grandson of the patient in Case 1 and son of the patient in Case 2 was brought to the clinic on Aug. 10, 1945, at the age of 4 years. The chief complaint was bilateral sinus tracts in the neck, which had been present since birth. The tracts had never been infected but a yellow mucoid material drained from them intermittently. Results of physical examination were normal except for bilateral pin-point openings under the mandible. The patient was seen in consultation by a surgeon but operation was not recommended at that time.

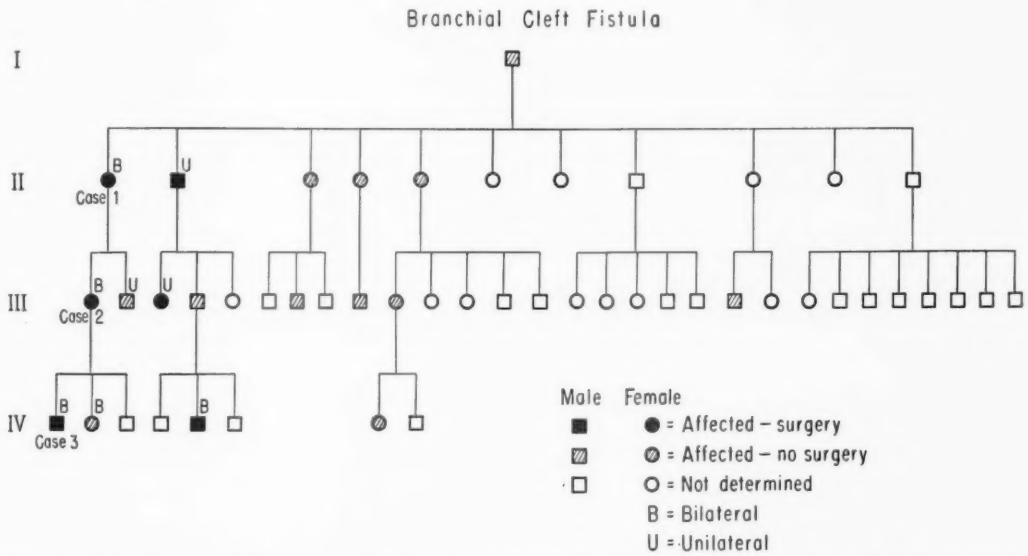

Fig. 3.—Inheritance of branchial fistula. In this family 18 of 49 members have had branchial fistulas, 5 cases being bilateral.

The patient returned with his grandmother on Aug. 7, 1957, when he was 16 years old. At this time he complained of daily drainage from the left fistula, which increased with eating and drinking. The fistula on the right side of the neck drained intermittently. Results of physical examination were negative except for a cervical fistula lateral to the thyroid cartilage on each side. The sinus tracts were palpable at this time. Results of routine urinalysis, stereoscopic chest roentgenogram, and examination of the blood were normal.

On Aug. 10, 1957, one of us (O. H. B.) excised the right and left branchial cleft fistulas. Elliptical incisions were made about the openings of each fistula and the tracts were traced into the neck along the sternocleidomastoid muscle, between the internal and external carotid arteries, over the hypoglossal nerve, and beneath the posterior belly of the digastric muscle. The tracts were ligated several millimeters from the tonsillar fossae. The pathologist reported bilateral branchial cleft sinuses lined by squamous epithelium with lymphoid tissue in the wall.

FAMILIAL TENDENCY

The family tree is presented in Fig. 3. The maternal great-grandfather of our patient in Case 3 transmitted the anomaly to 5 of his 11 children, one being a male. Each of those 5 transmitted the anomaly to one or all of his

children, who in turn passed it on to the fourth generation. At the time of this writing we know of 49 persons in this family tree and 18 have had branchial cleft fistulas. Five of the 18 have bilateral fistulas, and 4 patients among these 5 are directly related genetically.

One male in the second generation had a branchial fistula and he transmitted the anomaly to his children, one of whom in turn transmitted it to his children. Hyndman and Light[5] concluded that branchial fistula may be inherited through the mother only, but that generalization is not substantiated in this family, in which the anomaly was passed on through the males in 3 successive generations. Another interesting observation is the inheritance of the anomaly by a male of the third generation through a female of the second generation who did not have the anomaly.

SUMMARY

Three cases of bilateral branchial fistulas surgically treated have been presented. The patients were among 18 persons with branchial cleft fistulas in a single family, the anomaly having been inherited through both male and female members.

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OBSERVATIONS CONCERNING BACTERIAL DEFENSE MECHANISMS DURING HYPOTHERMIA

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THE suggested use of hypothermia in infection, as commented upon by Eiseman and co-workers,[5] depends upon a depression or retardation of bacterial metabolism and growth with a lesser effect upon the bacterial defense mechanisms of the host. From observations made by them in experimental pneumococcal peritonitis they concluded that this was so, although they presented no experimental evidence to support the claim. Balch, Noyes, and Hughes,[1] on the other hand, concluded from their experiments on peritonitis in the hypothermic rat that 2 physiologic effects are present in hypothermic animals—a less rapid bacterial proliferation and also a less efficient bacterial defense mechanism. Friedman, Davidoff, and Fine[11] have reported that hypothermia protects the antibacterial defense mechanisms ordinarily injured by hemorrhagic shock so that animals may cope with a dose of bacteria injected during the hypotensive period that would be fatal to normothermic dogs. Since cooled animals withstood the bacteria when injected after the body temperature was back to normal, in contrast to normothermic shocked animals, they concluded that suppression of bacterial activity by the hypothermia was not the only factor involved.

In this laboratory studies were undertaken[6] to determine whether a bacterial factor might not be present in the hypotension of prolonged hypothermia and subsequent rewarming which could account for the death of animals cooled for protracted periods of time. It was reported by us as a result of this work (1) that hypothermia even after many hours does not promote a state of bacteremia and (2) that the hypothermic animal is still capable of removing pathogenic organisms injected into the blood stream. Since it was demonstrated by Harmon and associates[13] that the phagocytic powers of the polymorphonuclear leukocytes decreased with lowered temperatures in vitro and since several investigators[2, 15, 22] have reported a profound luekopenia with hypothermia, the exact mechanism of bacterial removal remained obscure. It was suggested that perhaps the liver and spleen assume a major role in phagocytosis under these conditions. To further evaluate the antibacterial mechanism during hypothermia and following rewarming, leukocyte counts have been performed on animals cooled for as long as 8 hours and then returned to normothermia.

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*John and Mary Markle Scholar.

Phagocytic indices have been similarly determined, and electrophoretic patterns of serum have been obtained. A presentation of these observations is the subject of this paper.

METHODS

Healthy mongrel dogs of both sexes averaging 12 Kg. of weight and on a stock laboratory diet were used in this study. All animals were permitted water, but no food, for 12 hours preceding the experiment. Under local anesthesia a polyethylene catheter was placed via an external jugular vein into the right ventricle, and through this the preanesthetized control and all subsequent blood samples were drawn. Animals were anesthetized with open drop ether and subjected to surface cooling by submerging in a 4° C. water bath. The details of cooling, maintenance of hypothermia, and rewarming were standard for this laboratory and have been previously described.[8] All animals were maintained at a body temperature of 23 to 24° C. during the cooling period. Total white counts from oxalated blood by the standard technique and smears using Wright's stain were made upon withdrawal of blood. Phagocytic indices were determined by the method of Huddleson[16] with modifications by Harris.[14] A stock culture of *Escherichia coli,* prepared in advance from the dog's stool, was used. One-half milliliter of blood and 0.5 ml. of culture were incubated at 37° C. and at the animal's temperature for one hour. Smears similar to blood films for differential counts were then prepared. Phagocytic index numbers were obtained from the nomogram of Foshay and LeBlanc.[10] This index number represents an approximate expression of the capacity to phagocytose *Escherichia coli,* expressed in percentage of total potential capacity. Electrophoretic patterns of serum proteins were obtained utilizing paper electrophoreses as described previously in detail by one of us (E. R. F.).[3]

RESULTS

Leucocyte Counts.—Total white cell counts and differential smears were made on 17 dogs (Group A) before anesthesia, before placing the animals in the cold bath, after 1 and 4 hours of hypothermia, and then, as has been standard for rewarming experiments in this laboratory, 1, 5, 9, and 24 hours after the animal had reached 29° C. during its return to normothermia. In an additional 15 animals (Group B) hypothermia was maintained for 8 hours and observations were made at times similar to the 4-hour cooled group, except that an additional sample was taken just before rewarming (8 hours).

Total Count (Fig. 1).—A slight, but not significant, decrease in leukocytes occurred with ether anesthesia in both groups. At the end of one hour of hypothermia decreases of 70 per cent (Group A) and 69 per cent (Group B) in total counts occurred. These findings are similar to those of Villalobos[22] for animals cooled to 17° C. under Pentothal (average decrease of 80.1 per cent) and of Helmsworth[15] (86 per cent reduction of leukocytes) who used pentobarbital as the anesthetic agent. After 4 hours of hypothermia it was of interest to find that in both groups counts had begun to increase so that in Group

B by 8 hours of hypothermia two-thirds of the animals were either back to control level or above. Rewarming resulted in a prompt continued increase in total count to a peak in both groups 9 hours after rewarming.

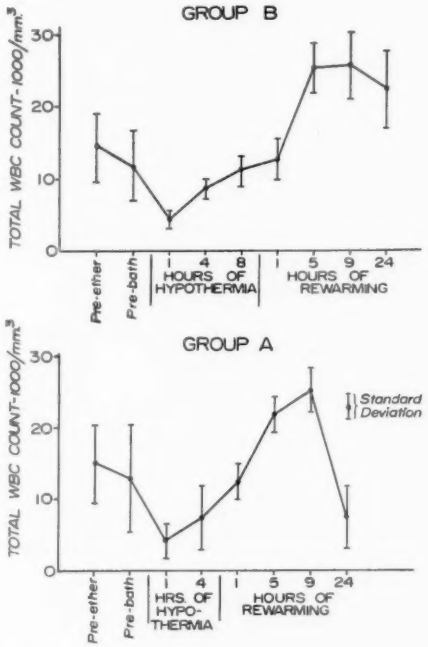

Fig. 1.—Total white blood count. Hypothermia (1, 4, and 8 hours) followed by rewarming.

Differential Counts (Table I).—

TABLE I. DIFFERENTIAL COUNTS DURING HYPOTHERMIA (1, 4, AND 8 HOURS) AND FOLLOWING REWARMING—PERCENTAGE OF NUCLEATED CELLS

	NEUTROPHILS		LYMPHOCYTES	EOSINOPHILS	MONOCYTES	ERYTHROBLASTS
	SEGMENTED	BANDED				
Group A						
Normothermia	57	10	25	7.0	0.3	0.7
Hypothermia						
1 hour	29	16	44	5.0	0.0	6.0
4 hours	31	25	31	6.0	0.0	8.0
Rewarmed						
1 hour	30	26	28	3.0	0.0	13.0
5 hours	40	48	9	1.0	0.0	2.0
9 hours	45	44	9	1.0	0.0	0.7
24 hours	44	38	15	1.0	0.0	1.0
Group B						
Normothermia	56	8	27	7.0	2.0	0.0
Hypothermia						
1 hour	31	11	45	7.0	0.4	5.0
4 hours	39	21	30	5.0	0.0	5.0
8 hours	39	24	26	6.0	0.0	5.0
Rewarmed						
1 hour	39	35	18	2.0	0.3	6.0
5 hours	48	41	7	0.6	0.2	3.0
9 hours	50	42	6	0.4	0.4	2.0
24 hours	42	48	9	0.9	0.1	0.4

Neutrophils: Control counts revealed 57 per cent segmented and 10 per cent band neutrophils. Upon cooling, the total number of neutrophils decreased almost parallel with the total white count. However, the type of neutrophil shifted. After 4 hours of cooling, 25 per cent of the cells in Group A and 21 per cent in Group B were banded. At the end of 8 hours of cooling (Group B), segmented neutrophils comprised 39 per cent of the total count and the band forms 24 per cent. Following rewarming a substantial increase in band forms occurred, so that by 9 hours after rewarming there were almost as many bands as segmental neutrophils present. This shift to the left persisted through the 24-hour period of observation after rewarming. Although there was demonstrated[7] an increase in hematocrit of 16 per cent in animals cooled 2 and 4 hours and 20 per cent in animals maintained hypothermic for 8 hours which might account for some of the increased WBC, an actual increase in the number of band neutrophils occurred in 14 of 17 animals, for after 4 hours of hypothermia there was a 21 per cent increase, after 8 hours a 90 per cent increase, and a 142, 733, 655, and 286 per cent rise 1, 5, 9, and 24 hours, respectively, subsequent to rewarming.

Lymphocytes: Villalobos[22] reported a relative rise in lymphocytes in only 1 of 6 dogs, whereas Helmsworth[15] reported a general increase. Our own results demonstrated that all but 2 animals had a relative increase in percentage of lymphocytes as determined from the blood smear. This was greatest after one hour of hypothermia, when lymphocytes comprised 44 per cent of the total white cell count as compared to 25 per cent before cooling. Insofar as actual numbers of lymphocytes, two-thirds of the dogs demonstrated a decrease during the cooling period which persisted during rewarming. What role is ascribed to the lymphocytes in the current thinking of phagocytic activity is still inconclusive. However, studies by Koszewski and co-workers[17] on the phagocytic activity of lymphocytes in human subjects intravenously injected with India ink indicate that human lymphocytes are capable of phagocytosis. It is reasonable to assume that this might well be true for the dog.

Eosinophil, monocytes, and erythroblasts: Although there was a decrease in the total number of eosinophils during hypothermia and rewarming, the percentage of these cells showed little change during cooling but decreased during rewarming. This eosinopenia can be correlated with a report by Fisher and associates[9] on the hypothermic rat in which a statistically significant decrease in adrenal weight, related to loss of water and solids, results with hypothermia and ether narcosis for 2 hours. Since these changes are not seen in the rat adrenal after 6 hours of hypothermia and ether anesthesia, "these findings have been interpreted as indicating that in the rat an initial stress is attendant with hypothermia when ether anesthesia is employed." Ganong[12] and Egdahl[4] report a diminished corticoid secretion in hypothermic dogs, but with the initial stress (placing the animal in cold water 3 to 4° C.) it is not amiss to expect an outpouring of adrenal cortical hormone resulting in an eosinopenic response which would persist during the observed period of hypothermia. Upon rewarming Ganong[12] reports an increase in concentration of corticoids, although

blood flow in some dogs did not reach prehypothermic levels. This outflow of suprarenal corticoids could account for the still lowered number of eosinophils following restoration of normal body temperature.

Little can be said of the monocytes. The few present in the precooling samples for the most part disappeared during cooling and rewarming.

As mentioned by Villalobos,[22] the number of erythroblasts were found to increase during hypothermia and more so following rewarming. Abnormal numbers of nucleated red cells were found as long as 24 hours after rewarming.

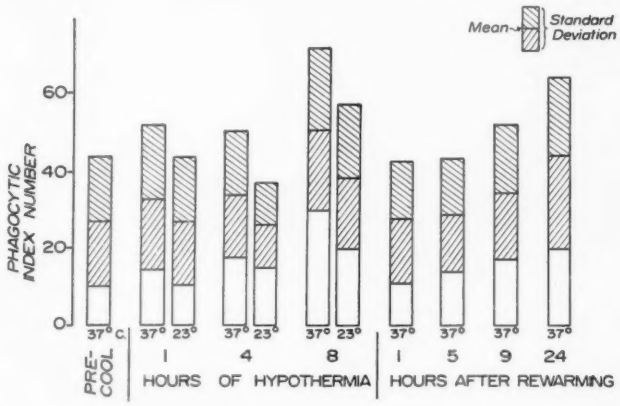

Fig. 2.—Phagocytic index number during hypothermia (23° to 24° C.) and after rewarming.

Phagocytic Index Number (Fig. 2).—Twelve animals cooled for 4 hours and rewarmed and 8 hypothermic for 8 hours and rewarmed were used for this phase of the study. Since data in the 2 groups of animals were similar, they are combined and presented as one. Extreme variation occurred in the phagocytic index number from animal to animal, as is reflected in the standard deviation. Values obtained during cooling and after rewarming were compared with the same animal before hypothermia. A precooling value of 27 ± 16.9 was obtained for the 20 animals. No significant difference occurred from this at 1, 4, or 8 hours of cooling or after rewarming. Further, no difference was noted between the phagocytic index numbers obtained from blood incubated at 23° C., the animal's temperature during hypothermia, and at 37° C. These findings are not in agreement with Harmon and co-workers,[13] who report a decrease in phagocytosis with lowered temperatures. However, the 2 experiments are not similar in that Harmon studied leukocytes recovered from exudates of the peritoneal cavity and the time allowed for exposure of leukocytes to lower temperatures was shorter. Lerner,[18] comparing blood and exudate leukocytes, finds a significantly increased capacity of blood leukocytes for phagocytosis of pneumococci. Madsen and Wulff[19] state that for phagocytosis, in vitro, the optimum temperature is that of the animal's body at the time the cells are withdrawn; this would be in agreement with our findings. However, this concept could not explain why phagocytosis was not significantly different between samples incubated at the animal's body temperature during hypothermia and

at 37° C. Perhaps incubation for a longer period of time, that is 4 or 8 hours, permits the leukocytes to acclimate to the lowered temperature and phagocytize normally. Further investigation of this supposition is in order.

Electrophoretic Patterns (Per Cent of Total Plasma Protein).—It has been reported by us[8] that no decrease in plasma proteins occurs in hypothermia of short duration, but that with a prolongation of cooling there is a decrease in this value. Animals cooled 4 and 8 hours do not show a decrease in plasma proteins. In view of the work by Tullis and Surgenor[21] on the phagocytosis promotion factors (PPF) which were identified as a β-globulin fraction and an α-1 globulin factor, it was imperative to determine whether there was a depletion or shift of these components during hypothermia and subsequent rewarming. Table II represents our findings which indicate no statistical difference throughout the experimental period in the protein fractions. Thus, it would seem that the PPF factor is present at all times.

TABLE II. PERCENTAGE OF TOTAL PLASMA PROTEIN

	NORMOTHERMIA	HYPOTHERMIA (HOURS)				AFTER REWARMING (HOURS)			
		2	4	6	8	1	5	9	24
Albumin	36.2 ±7.7	38.8 ±9.4	37.6 ±10.4	37.5 ±9.9	35.7 ±7.3	37.0 ±8.9	39.1 ±10.8	41.8 ±10.0	39.6 ±6.8
Globulin									
Alpha	13.4 ±2.5	13.7 ±2.5	14.1 ±2.3	14.4 ±2.7	17.9 ±3.5	15.8 ±2.7	15.7 ±2.7	12.3 ±2.2	17.2 ±2.8
Beta	38.0 ±10.7	35.9 ±12.7	36.2 ±9.3	32.9 ±7.7	35.3 ±9.5	37.9 ±13.7	34.2 ±9.2	32.4 ±8.9	31.5 ±5.1
Gamma	12.2 ±6.1	11.5 ±5.1	12.1 ±5.0	10.2 ±4.3	10.5 ±3.2	9.3 ±4.0	10.8 ±7.1	13.3 ±7.2	11.5 ±7.5

DISCUSSION

A previous report[6] from this laboratory showed that hypothermic animals injected with 5 billion to 50 billion bacteria (*Escherichia coli* and *Aerobacter aerogenes*) were able to rid the blood within 6 hours of 99 per cent of the injected pathogens. However, unlike the normothermic animals which cleared the blood completely by 24 hours, some of the cooled animals still demonstrated a bacteremia. At that time we attributed this incomplete clearance to (1) a leukopenia, (2) decreased phagocytic powers of remaining leukocytes, and (3) a trapping and intermittent release of contaminated blood, as well as a decreased blood flow to phagocytic centers, that is, liver and spleen. In the light of the present experiments it would seem that 2 of these premises can be discounted. Leukopenia does exist, but only for a transitory period after which leukocytes are back to normal or shift to the left due to an outpouring of band neutrophils. The reason for this influx of band forms is not known, but they are available for phagocytosis even though Matoth[20] points out that neonatal neutrophils show less phagocytosis as compared with adult cells in vitro. A decrease in phagocytic powers of leukocytes at lowered temperature is not consistent with these experiments. We do not contest the findings of Harmon and co-workers[13] but attribute differences to experimental procedure. Therefore,

a trapping and intermittent release of contaminated blood as well as a decreased blood flow to phagocytic centers seem to be the most obvious reason why hypothermic animals, innoculated with bacteria, do not clear the blood stream as efficiently as normothermic animals. The PPF factor, as described by Tullis,[21] is evident and, therefore, available to convert the phenomenon of phagocytosis "from an interesting laboratory demonstration to a rapidly consummated biologic phenomenon exerting significant effect upon host survival." Thus, it would seem that, with an inhibition of bacterial multiplication during hypothermia, as indicated by Eiseman and associates[5] and a maintenance of immunologic response as indicated by these experiments during cooling and rewarming, the rationale for the use of hypothermia in combating infection is reasonable. Of practical clinical significance is the finding that bacterial defense mechanisms are maintained following rewarming. In this laboratory the physiologic effects of hypothermia have been observed over protracted periods of time and at body temperatures lower than those in use in the clinic, for it is felt that if no untoward effects of hypothermia are found at these extremes, none should occur at the higher temperatures of shorter duration used in clinical practice.

SUMMARY AND CONCLUSIONS

The effects of hypothermia and subsequent rewarming upon some of the factors influencing bacterial defense mechanisms have been described. It has been observed that: (1) the leukopenia characteristically described in hypothermia is transitory in nature and is followed by a leukocytosis resulting from a marked increase in band neutrophils, (2) no reduction in phagocytosis of blood leukocytes was evident either during hypothermia or following rewarming, and (3) electrophoretic patterns of plasma demonstrated no change in phagocytic promotion factors (PPF).

These observations indicate that the bacterial defense mechanisms evaluated are not depressed during hypothermia and subsequent rewarming and that the rationale for the use of hypothermia in combating infection is reasonable.

The technical assistance of James Dattilo and Elizabeth Saffer is gratefully acknowledged.

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EXPERIMENTAL OPEN HEART SURGERY EMPLOYING HYPOTHERMIA, MECHOLYL ARREST, AND CAROTID PERFUSION

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INTRODUCTION

THE obvious advantages of operating within the bloodless heart have greatly intensified interest and experimentation on methods and techniques which facilitate it. One method by which this long-sought goal has been reached is hypothermia. The essential advantage of this approach is simplicity. The disadvantage is that hypothermia alone will not suffice should prolonged periods of circulatory arrest be required. Another major avenue of effort has been the use of a mechanical heart-lung machine. The essential advantage of this approach is that such a system can substitute for the heart and lungs allowing the time required for definitive repair of the lesion. The disadvantages are the need for major team effort and the hazards imposed by the pump-activation and oxygenation of large quantities of blood. The experiments described below were initiated in the hope of attaining an approach which would provide the operative time needed without the attendant complexities of pump-oxygenation. The basic components of this approach are the combination of hypothermia and cardiac arrest induced by Mecholyl *(acetyl-β-methylcholine chloride) for a 15- to 20-minute period with the addition of carotid perfusion when more prolonged periods of cardiac exclusion were intended.

METHODS

Healthy mongrel dogs weighing from 9 to 17 Kg. were used. The intramuscular administration of 1 mg. per kilogram of Phenergan was given as premedication one hour before anesthesia was induced with 25 to 30 mg. per kilogram of sodium pentobarbital given intravenously. Intermittent positive pressure with air was applied through an endotracheal tube. Femoral artery pressures were obtained through a Statham strain gauge and registered with the electrocardiogram (Lead II) on a Sanborn recorder. Hypothermia was then induced by immersion in an ice bath until a rectal temperature of 33° to 34° C. had been attained. A further fall of 3° to 5° C. subsequently occurred so that the rectal temperature was 28° to 30° C. during circulatory arrest. In a few instances shivering occurred and was controlled by brief periods of ether administration.

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Thoracotomy was performed through the fourth right intercostal space. The azygous vein was ligated and umbilical tapes loosely placed around the superior and inferior venae cavae. The pericardium was opened widely. All dogs then received 1.5 mg. per kilogram of heparin intravenously. In the experiments in which carotid perfusion was intended, plastic catheters were secured in the proximal end of the right subclavian artery, the branches of which had previously been ligated, and in the superior vena cava via the azygous vein as shown in Fig. 1.

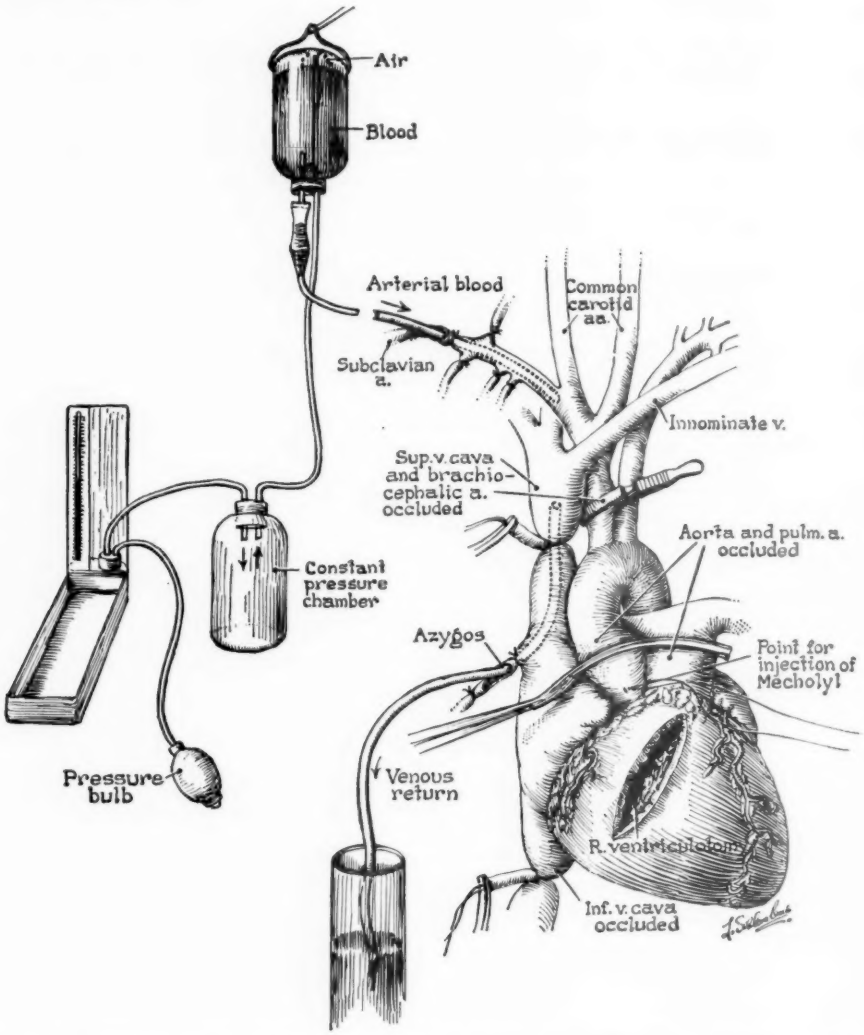

Fig. 1.—Schematic representation of the perfusion system during cardiac exclusion.

Circulatory standstill was accomplished by occlusion of both venae cavae, and about one minute was allowed for partial cardiac emptying before the aorta and pulmonary artery were cross-clamped. Immediately thereafter 1.2 to 1.4 mg. per kilogram of Mecholyl, diluted in 6 c.c. of saline, was rapidly injected into the root of the aorta to induce cardiac arrest. Artificial respiration was

discontinued with consequent deflation of the lungs. In the 14 experiments of group A (Table I) carotid perfusion was not used. A 5 cm. right ventriculotomy was performed in 10 of these and a 2 to 3 cm. ascending aortotomy in 4. During closure the heart was filled with saline to avoid air emboli. These incisions were later repaired just before restoration of the heart's action. The latter was initiated by the use of a solution containing 2 mg. of atropine and 0.5 mg. of epinephrine in 6 ml. of saline. Of this volume, 4 ml. was injected into the root of the aorta and 2 ml. into the right atrium. Cardiac massage was started and after 8 to 10 mannual compressions, the aorta, pulmonary artery, and superior vena cava were opened. Simultaneously artificial respiration was restarted. Massage was continued and fibrillation usually resulted. This was observed to be quite vigorous in character and readily restored to sinus rhythm with the first attempt at defibrillation (125 volts, 0.1 sec.); occasionally a second shock was required. As soon as the heartbeat was restored the inferior vena cava was released.

TABLE I. GROUP A. MECHOLYL ARREST WITHOUT CAROTID PERFUSION

DOG NUMBER	DOG WEIGHT (KG.)	TEMPERATURE (° C.)	TIME CARDIAC EXCLUSION (MIN.)	RESULT
1	13.0	30.0	15	Alive and well
2	11.8	27.0	18	Alive and well
3	10.7	27.5	18	Alive and well
4	12.5	31.0	16	Alive and well
5	12.5	30.0	21	Severe neurologic damage
6	11.8	28.5	17	Alive and well
7	11.5	28.0	16	Alive and well
8	10.5	28.0	17	Expired due to hemorrhage
9	12.5	29.0	24	Failed to awaken, expired within 24 hours
10	13.5	29.0	25	Failed to awaken, expired within 24 hours
11	9.0	28.0	18	Alive and well
12	12.5	28.0	30	Failed to awaken, expired within 24 hours
13	13.5	29.0	15	Alive and well
14	14.5	28.0	17	Alive and well

In the 20 dogs in group B (Table II) longer periods of circulatory standstill were imposed. This was accomplished as described above with the addition of occlusion of the brachiocephalic artery and institution of carotid perfusion immediately after circulatory arrest. The blood for perfusion had been collected by the arterial bleeding of only locally anesthetized donors to which 3 mg. per kilogram of heparin had been administered intravenously. Perfusion was through a standard filter recipient set from an overhanging transfusion bottle and entered the carotid arteries via the subclavian catheter. The rate of administration (1.3 to 3.6 c.c. per kilogram per minute) was controlled by the appropriate adjustment of the pressure chamber by means shown in Fig. 1. Blood returning from the brain was collected by gravity drainage into a graduated cylinder on the floor via the superior vena caval catheter. The volumes of blood recovered in this manner were always essentially the same as the volumes introduced. After carotid perfusion was begun a 5 cm. right ventriculotomy was performed in all dogs of this group and in two a 2 to 3

cm. ascending aortotomy was also done. These incisions were later repaired just prior to cessation of carotid perfusion. The latter was accomplished by first occluding the superior caval drainage catheter, and after allowing a further

TABLE II. GROUP B. MECHOLYL ARREST WITH CAROTID PERFUSION

DOG NUMBER	DOG WEIGHT (KG.)	TEMPERATURE (° C.)	TIME CARDIAC EXCLUSION (MIN.)	RATE BLOOD PERFUSED (C.C. PER KG. PER MIN.)	OXYGEN SATURATION (%)		RESULT
					BLOOD PERFUSED	VENOUS RETURN	
15	12.8	29.5	33	1.7	95	36	Alive and well
16	13.8	29.0	33	1.3	91	37	Transient ataxia
17	13.1	29.0	43	2.2	88	45	Alive and well
18	10.8	29.0	44	1.8	94	36	Alive and well
19	10.0	29.0	35	2.9	95	41	Alive and well
20	11.8	28.0	33	2.7	95	32	Alive and well
21	13.6	29.0	43	2.3	96	34	Alive and well
22	14.2	29.0	32	2.4	94	42	Alive and well
23	9.0	28.0	33	3.6	87	42	Alive and well
24	10.0	29.0	34	3.4	98	31	Alive and well
25	13.8	29.0	32	2.4	100	47	Alive and well
26	11.7	30.0	35	3.1	100	43	Alive and well
27	13.5	29.0	44	2.2	94	42	Alive and well
28	11.4	30.0	44	2.7	100	37	Alive and well
29	11.0	27.5	44	3.1	99	48	Died eighth day, empyema
30	13.6	29.0	45	2.4	90	39	Alive and well
31	10.0	29.0	44	3.4	100	38	Alive and well
32	14.8	29.5	38	2.8	92	34	Alive and well
33	16.8	30.0	50	2.4	96	40	Alive and well
34	14.0	30.0	49	2.7	92	37	Alive and well

TABLE III. GROUP C. POTASSIUM ARREST WITH CAROTID PERFUSION

DOG NUMBER	DOG WEIGHT (KG.)	TEMPERATURE (° C.)	TIME CARDIAC EXCLUSION (MIN.)	RATE BLOOD PERFUSED (C.C. PER KG. PER MIN.)	AMOUNT K USED (C.C.)	TIME-VENTRICULAR RECOVERY (MIN.)	RESULT
35	11.7	30.0	34	2.7	7	-	Unable to resuscitate in 25 minutes
36	12.5	30.0	40	2.2	10	-	Unable to resuscitate in 25 minutes
37	12.0	30.0	32	2.8	12	18	Alive and well
38	11.5	29.0	29	2.5	8	21	Failed to awaken, expired within 24 hours
39	11.4	30.0	31	2.6	14	16	Alive and well
40	14.0	29.0	39	3.0	8	21	Failed to awaken, expired within 24 hours
41	13.6	29.0	38	2.5	14	-	Unable to resuscitate in 25 minutes
42	14.3	30.0	33	2.8	9	13	Alive and well
43	10.7	28.0	44	2.2	11	-	Unable to resuscitate in 25 minutes
44	10.0	29.0	30	3.1	11	14	Alive and well

arterial infusion of 100 to 200 c.c. to cover operative loss the perfusing catheter was occluded. Immediately thereafter artificial respiration was restarted and reconstitution of the heart's activity accomplished as described above. The perfusion and drainage catheters were removed and 3 mg. per kilogram of protamine was given intravenously. The chest was closed with a catheter in the pleural cavity for intermittent suction as required. Rewarming to a rectal temperature of 37° C. was accomplished in a water bath at 45° C.

The 10 dogs in group C (Table III) were treated similarly to those in group B except that a 2.5 per cent potassium citrate solution (0.23 mEq. per cubic centimeter) was used to induce arrest. This solution was injected into the root of the aorta until arrest occurred. During recovery of the heart's activity an equivalent amount of calcium chloride was used in 6 dogs and 50 per cent glucose was used in 4 dogs to enhance contractions. If this failed, 3 to 6 c.c. of a 0.1 per cent solution of epinephrine was given.

All dogs received antibiotics for the first 3 to 5 days postoperatively.

RESULTS

Group A. Mecholyl Arrest Without Carotid Perfusion.—There were 14 dogs in this group with temperatures ranging from 27° to 31° C. and periods of cardiac exclusion from 15 to 30 minutes (Table I). Ten of the dogs had circulatory arrest for periods of 15 to 18 minutes. Nine of these were alive and well at the end of a 6-week period of observation. The tenth expired following hemorrhage from the aortotomy incision. Of the 4 dogs that had occlusion longer than 18 minutes one, occluded 21 minutes, had severe permanent neurologic damage. The remaining 3, occluded 24, 25, and 30 minutes, failed to awaken and expired in the early postoperative period. Sinus rhythm began without fibrillation in 3 dogs, but defibrillation was required for recovery in 11. A single shock was required in 9 instances and a second shock in 2 instances. The characteristics of the Mecholyl-arrested heart are described below.

Group B. Mecholyl Arrest With Carotid Perfusion.—There were 20 dogs in this group with temperatures ranging from 27.5° to 30° C. and periods of cardiac exclusion from 32 to 50 minutes (Table II, Fig. 2). The carotid perfusion rates ranged from 1.3 to 3.6 c.c. per kilogram per minute. Oxygen saturations done on a Woods oximeter averaged 93 per cent for the blood perfused and 39 per cent for the venous return. Nineteen of the 20 dogs were alive and well at the end of a 6-week period of observation. The remaining dog expired on the eighth postoperative day with empyema. Another dog exhibited transient ataxia during the first postoperative day. No other evidence of neurologic damage was observed.

The effects of Mecholyl when used as described presented a characteristic pattern. Spontaneous cardiac activity ceased after the injection of Mecholyl and about one minute later weak ventricular contractions began. These promptly diminished in amplitude so as to become almost unnoticed by the casual observer and in no way hindered operative manipulation. The heart remained flaccid and of good color throughout occlusion. There was no active blood loss

from the open heart. Ventricular complexes occurred at a regular but decreasing rate and averaged 10 per minute (Fig. 2, *D* and *E*). Mechanical stimulation often gave rise to a weak ventricular contraction during the first 2 to 3 minutes after the injection of Mecholyl and thereafter caused only a rare and very weak contraction. In 3 instances, spontaneous contractions were almost entirely absent throughout occlusion. During brief periods contraction could not be seen although ventricular complexes were recorded. There was no visual or electrocardiographic evidence of atrial activity.

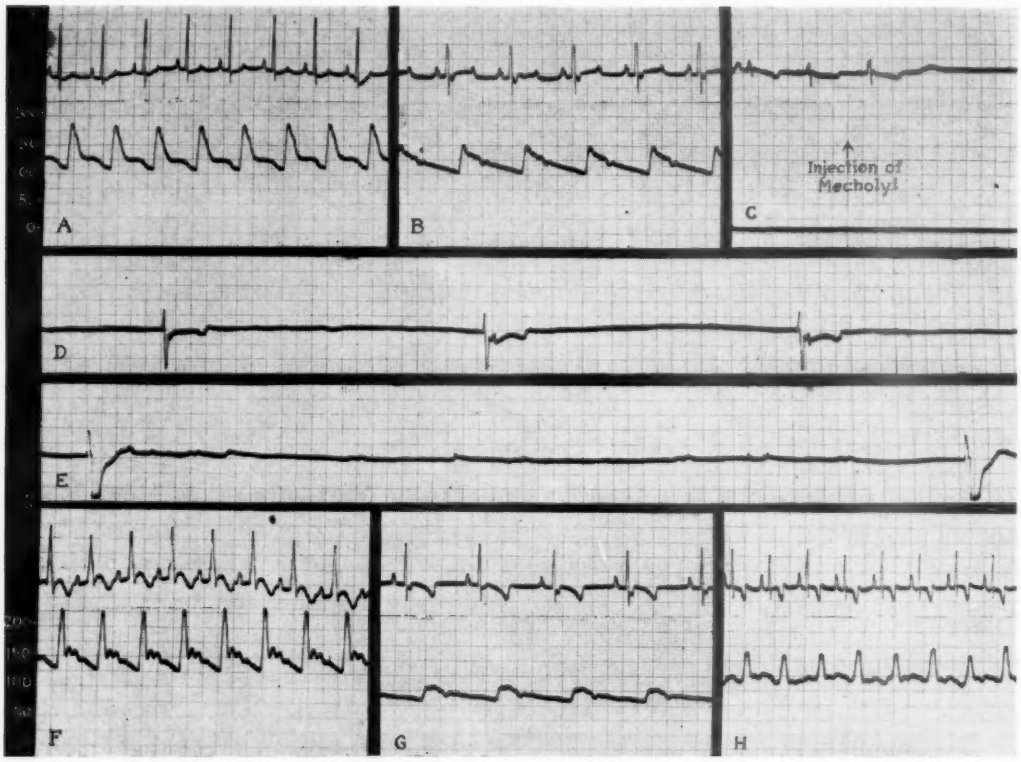

Fig. 2.—Dog No. 33. Electrocardiographic (Lead II) and blood pressure tracings before, during and after 50 minutes of circulatory arrest utilizing hypothermia, Mecholyl, and carotid perfusion. *A*, Normothermia. *B*, Hypothermia (30.5° C.). *C*, Induction of Mecholyl arrest. *D*, Electrocardiogram after 15 minutes of circulatory arrest and, *E*, after 45 minutes of circulatory arrest. *F*, Sinus rhythm one minute after release of occlusion. Note the high blood pressure and heart rate after atropine and epinephrine. *G*, After the chest is closed (30° C.). *H*, After rewarming to 37° C.

Restoration of the heart's activity resulted in a strong fibrillation in 18 instances and sinus rhythm in 2. The ease of defibrillation followed by a sinus rhythm and vigorous beat was striking. A second shock was required in 3 dogs and a third shock in one dog. The average blood pressure was 176/98 twenty to thirty seconds after defibrillation. The high blood pressure and heart rate that resulted soon fell to levels expected for the degree of hypothermia (Fig. 2, *F* and *G*). There were no further arrhythmias once sinus rhythm was re-established. The average time from the release of occlusion to return of sinus rhythm was 1.2 minutes and ranged from 0.5 to 4 minutes.

Group C. Potassium Arrest With Carotid Perfusion.—There were 10 animals in this group with temperatures ranging from 28° to 30° C. and periods of cardiac exclusion from 29 to 44 minutes (Table III, Fig. 3). The carotid perfusion rates ranged from 2.2 to 3.1 c.c. per kilogram per minute. Two dogs failed to awaken and expired in the early postoperative period. Four dogs developed persistent right-sided dilatation with intractable fibrillation despite massage and drugs and could not be resuscitated within a 25-minute period.

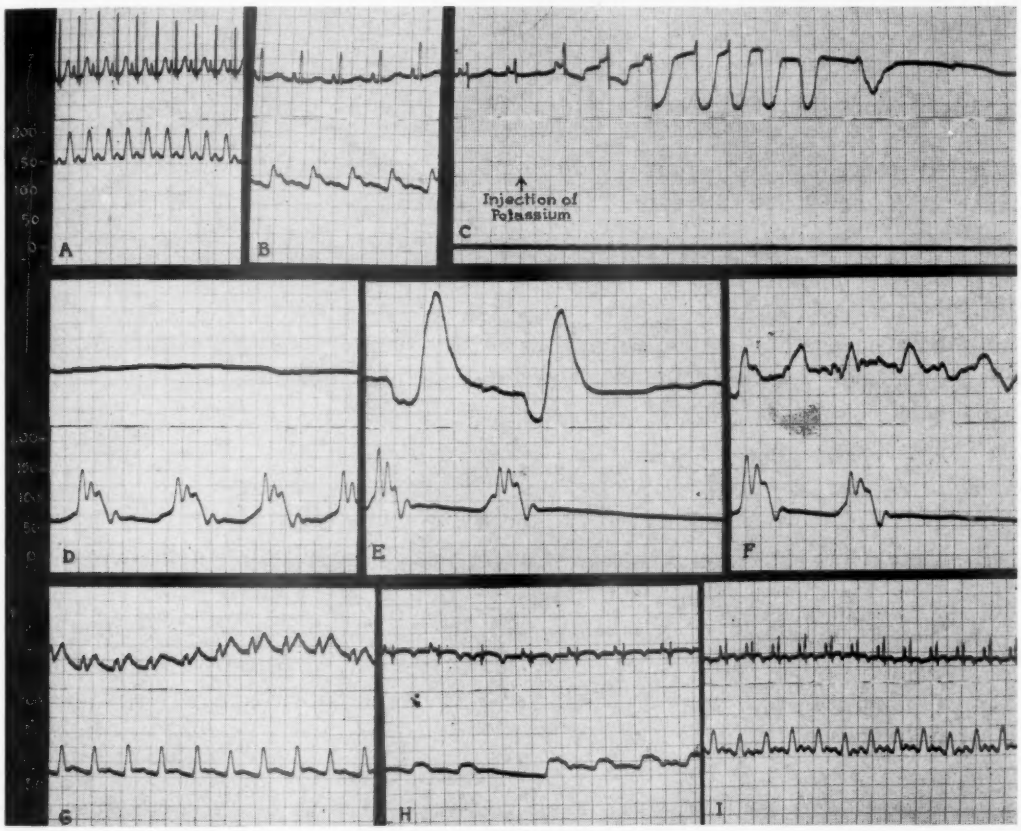

Fig. 3.—Dog No. 39. Electrocardiographic (Lead II) and blood pressure tracings before, during, and after 31 minutes of circulatory arrest utilizing hypothermia, potassium, and carotid perfusion. *A*, Normothermia. *B*, Hypothermia (30° C.). *C*, Induction of potassium arrest. *D*, The blood pressure tracings are the result of manual cardiac massage at 4 minutes after release of occlusion. There is no electrocardiographic evidence of activity. *E*, Cardiac massage 7 minutes after release of occlusion. There is a coarse contraction wave occurring with each manual compression. *F*, Cardiac massage 11 minutes after release of occlusion. The ventricles have regained the ability to generate spontaneous impulses. *G*, Recovery of the heartbeat following defibrillation 16 minutes after release of occlusion. *H*, The chest is closed (30° C.). *I*, After rewarming to 37° C.

Four dogs were alive and well at the end af a 4-week period of observation. A difference in the ability to strengthen the heart's contractions was not noted when either calcium chloride or 50 per cent glucose was used.

The potassium-arrested heart was devoid of irritability or conductivity. Resuscitation from this cardioplegic state with massage was prolonged and not always successful. During the first 3 to 7 minutes of massage the heart remained quiescent, and then a coarse contraction wave occurred with each manual

compression before the heart would generate spontaneous impulses (Fig. 3, *D, E,* and *F*). Ventricular recovery was initiated by defibrillation and began as an idioventricular rhythm in 4 instances and a sinus rhythm in 2. The average time from release of occlusion to ventricular recovery was 16 minutes and ranged from 14 to 21 minutes.

DISCUSSION

In these experiments 2 components were added to prolong the safe period of circulatory arrest afforded by general hypothermia. These were the protection against cerebral damage by carotid perfusion and a further reduction in cardiac metabolic activity by arresting the heart with Mecholyl. The rapid restoration of the heart's activity, which is essential for this approach, can then be accomplished with atropine since it completely abolishes the cardiac depressant effects (muscarinic) of Mecholyl. Mecholyl was used rather than another choline ester, since it possesses greater potency and selectivity in evoking cardiovascular responses.[1] Acetylcholine has been effectively used for elective cardiac arrest by Moulder[5] and Sergeant[6] and their co-workers. It was felt that a cardiotonic agent would aid in the recovery of the heart's activity and epinephrine was used for this purpose. In retrospect the latter was probably a poor choice in view of its tendency to produce arrhythmias. Although the fibrillation produced by the large dose of epinephrine was readily reversible in each instance, it would obviously be desirable to restore cardiac activity without fibrillation. An agent, such as Isuprel or Wyamine (mephentermine sulfate), which has a strong cardiotonic effect but lacks the tendency to produce fibrillation, may have been a wiser choice. Potassium, in contrast to Mecholyl, abolishes conductivity and irritability, and there is no known single agent which will rapidly and completely reverse this effect. Resuscitation of the potassium-arrested heart depends mainly upon lowering the myocardial concentration of this ion by coronary perfusion. When the latter is accomplished by cardiac massage, restoration of the heart's activity, as noted here and by others,[2-4, 7] is more prolonged and uncertain than would be desired in the procedure described.

The technique described above allows surgical attack upon either side of the heart as well as the coronary vessels. The control of blood volume is facilitated since there is no active blood loss from the open heart, nor are any volume changes introduced due to the carotid perfusion.

These studies indicate that carotid perfusion with the simple expedient of an infusion flask can protect against cerebral damage and that rates of 1.7 c.c. per kilogram per minute or above are adequate to accomplish this. The one dog which showed transient neurologic damage was the one with the lowest rate of perfusion (1.3 c.c. per kilogram per minute). Perhaps lower perfusion rates might have been used had the left vertebral artery been temporarily occluded in view of the possibility of retrograde loss of perfusing blood through this vessel at the circle of Willis.

SUMMARY

An experimental approach for open heart surgery was employed using hypothermia, Mecholyl arrest, and carotid perfusion. The use of Mecholyl and atropine for arresting and rapidly restoring cardiac activity is described. Three groups of experiments were done. In group A carotid perfusion was not used. There were 14 dogs in this group with temperatures ranging from 27° to 31° C. and periods of circulatory arrest from 15 to 30 minutes. When circulatory arrest exceeded 20 minutes the dogs failed to awaken and expired in the early postoperative period. In group B longer periods of circulatory standstill were imposed and carotid perfusion was used. There were 20 dogs in this group with temperatures ranging from 27.5° to 30° C. and periods of circulatory arrest from 32 to 50 minutes. The carotid perfusion rates ranged from 1.3 to 3.6 c.c. per kilogram per minute. These dogs all survived except one which expired on the eighth postoperative day with empyema. A transient ataxia noted in the dog with the lowest perfusion rate was the only evidence of neurologic damage. In group C potassium rather than Mecholyl was used to induce cardiac arrest. This group of experiments demonstrated that restoration of the potassium-arrested heart by the procedure described is uncertain and more prolonged than would be desired.

This approach permits surgical attack on either side of the heart and coronary vessels in a bloodless field and without annoying cardiac or respiratory movements. Although further work is probably needed before such a method is used clinically it does demonstrate that the time required for the definitive repair of intracardiac lesions may be attained by means simpler than extracorporeal circulation.

We gratefully acknowledge the technical assistance of Julius Mayo.

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INTRAVASCULAR PRESSURE CHANGES IN THE CAROTID SYSTEM FOLLOWING LIGATION OF THE COMMON AND EXTERNAL CAROTID ARTERIES

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THIS is a report of some observations made in the arterial pressure and pulse pressure, intravascularly, during various occlusions of the carotid system. The study has been carried out on 8 patients who had common carotid artery occlusion, 5 of them for aneurysms and 3 for fistulas. At the time of operation the common carotid artery and the internal and external carotid arteries were dissected. The superior thyroid was identified in the external carotid system. A No. 25 needle was inserted in the common carotid artery just below the bifurcation and readings were obtained with the Sanborn string gauge manometer. This apparatus works on the basis of a galvanometer and records direct arterial pressures accurately. Different parts of the carotid system were then occluded and recordings obtained of the pressures as affected by the occlusion.

It has been noted that upon occluding the external carotid artery below the origin of the superior thyroid artery the pressure showed a small rise, fluctuating from 5 to 25 mm. Hg. The pulse pressure remained the same, and the pulse rate showed a negligible increase (Fig. 1 and Table I).

Table I

PATIENT	COMMON CAROTID	EXTERNAL LIGATED	COMMON AND EXTERNAL LIGATED	PER CENT REDUCTION
E. P.	100/75	100/70	55	37
N. K.	100/70 100/90 150/125	115/80	25	70
D. W.	125/105	120/105	50	56
B. W.	160/125	170/140	45	68
C. V.	125/90	125/95	65	39

The next reading was that which followed occlusion of the common carotid artery with the aid of the Selverstone clamp. The most marked change at that time was the obliteration of the pulse pressure in association with a marked drop of the arterial pressure. Calculated on the basis of mean arterial pressures, the drop had fluctuated between 37 and 70 per cent of the original pressure. It had been noted during this stage of the procedure that the effects described above appeared rather dramatically at a specific turn during the clamping of the Selverstone clamp. For example, in one case no change was noted for 2½ full turns. During the next full turn (from 2½ to 3½ turns), the pressure dropped from 150/125 to 125/100 at the third turn and to 60 at 3½ turns.

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The damping of the pulse pressure (Fig. 1) did not become apparent until the completion of the 3½ turns. The remaining turns of the closure of the clamp produced only a minimal further reduction of the arterial pressure.

The last step in the procedure was the ligation of the external carotid below the origin of the superior thyroid after complete occlusion of the common carotid. It has been noted with this last maneuver that the arterial pressure was further reduced by 10 to 20 mm. These observations presented 2 facts that are applicable to the clinical management of patients needing carotid ligation.

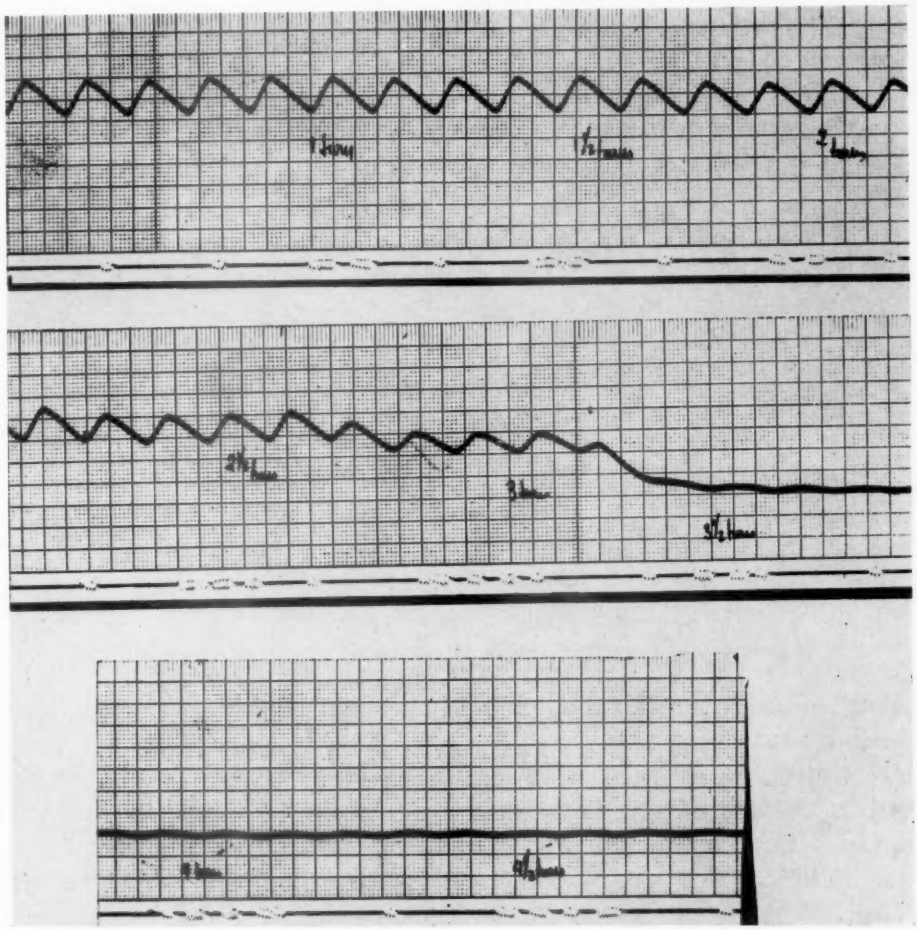

Fig. 1.—Intravascular pressure changes during the closure of the clamp.

First is the point of gradual occlusion. It has been a standard procedure to close a Selverstone clamp by turning one-half to one turn daily until complete occlusion was attained. Our tracings show that in such a situation no appreciable reduction of pressure is obtained with the first turns and that all the reduction will appear at a specific point in the closure of the clamp. By obtaining the reading on the operating table, the first ineffective turns were done in the operating room and the critical turn was carried out in increments of one-fourth turn or even slower, thus allowing an actual slow reduction of

pressure. After the critical turn it is no longer necessary to proceed on the basis of one-half turn and the rest of the clamping can be carried out at once.

The second observation is the one which is thought to be the most important and this is the fact that not only reduction of arterial pressure is obtained but also the complete damping of the pulse pressure.

Therefore in summary, we are obtaining (1) reduction of mean arterial pressure and (2) damping of pulse pressure.

It is only logical to assume that the reduction of mean arterial pressure will reduce the possibility of rupture of an aneurysmal wall strictly on the basis of pressure dynamics. Black and German[3] report a reduction of rupture incidence to 6 per cent following carotid ligation. The damping of the pulse pressure can be considered as a disadvantage because it has been proved experimentally that a continuous pressure is more likely to produce saccular formations in the form of varicosities. This has been reported and discussed in many

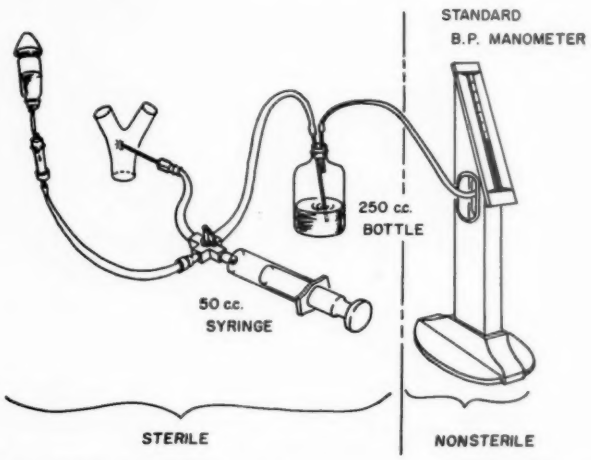

Fig. 2.—Apparatus for measuring intravascular pressure during surgery.

papers. However, the fact that the mean arterial pressure is reduced by 37 to 70 per cent neutralized that possibility. Walker and Allegre[12] report that there were complications in situations where the arterial pressure was not sufficiently reduced. The use of the Selverstone clamp also diminishes the likelihood of aneurysmal formation at the site of ligation. It has been reported by various investigators that the important point in ligating major arteries lies in producing minimal damage to the tunica muscularis and the elastic fibers. Gross and Holzman reported a case in which a large aneurysm appeared in the neck at the site of ligation of the common carotid 12 months after surgery. They had used silk ligatures. Round ligatures will produce such damage while the flat Selverstone surface will diminish such injury to tissues.

We have made it a point always to place our ligature on the external carotid below the origin of the superior thyroid or whenever this was not possible to ligate the superior thyroid separately. The collateral circulation of the superior thyroid is considerable and, particularly after ligation of the common carotid, it can act as a direct channel bringing blood from the opposite side.

We have had one such case that illustrates the point well. A patient with an arteriovenous fistula had the common carotid artery ligated as one procedure without relief of the bruit in his head and exophthalmos. As a second procedure the external carotid was ligated but the signs and symptoms recurred promptly. The symptoms did not disappear until the third procedure was done, which revealed that the superior thyroid artery had its origin at the bifurcation and therefore was not kept out of the system at the time of the second procedure.

On the basis of our findings we would like to make the following recommendations when ligation of the common carotid artery is carried out.

1. Use a Selverstone clamp or any other flat type of occlusive material but not a round ligature.

2. Some means of recording pressures should be used at the time of operation so as to ascertain the critical turn in the arterial occlusion. This will make the procedure safer and reduce unnecessary hospital days. It is not necessary to use an expensive apparatus for such readings. The accompanying sketch shows a simple, inexpensive way of obtaining such readings (Fig. 2). Some investigators suggest that ligation should not be done if there is a reduction below 30 per cent of the original pressure because the incidence of complications rises sharply after that point.

3. Last, the ligation on the external carotid must occur below the origin of the superior thyroid artery or, in the case of an anatomically aberrant superior thyroid, this vessel should be tied separately.

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BLOOD TURNOVER RATES DISTAL TO AN ARTERIOVENOUS FISTULA

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ALTHOUGH they are rather rare clinical entities, congenital and traumatic aneurysms were early recognized (Valsalva,† in the very beginning of the eighteenth century and Hunter† in 1757) and thoroughly investigated in the hospital ward and in the experimental laboratory.

Proximal arterial dilatation, proximal and distal venous dilatation, and narrowing of the artery beyond the fistula were described by Hunter in 1762.[16] He also noted a systolic murmur (''hissing noise'') over the arteriovenous shunt and a ''tremulous jarring motion'' in the vein. Amussat (1843)[1] is considered the father of the experimental physiology in this particular field. Of more interest is the work of Vignolo (1902)[29] and of Franz (1905).[10] On dogs, both of them successfully used the technique of anastomosing 2 vessels described first by San Martin y Santrustegui,[25] and, besides an accurate description of the local phenomena, they obtained interesting sphygmomanometric and thermometric recordings distal to an arteriovenous anastomosis.

Secondary effects on hemodynamics and the heart after opening an arteriovenous shunt were extensively studied by Holman[13] in 1924. An explanation was given of the bradycardic response on closure of an arteriovenous anastomosis (Nicoladoni-Branham phenomenon). More recently Frank and Wegria,[9] using a variable-at-will bypass between aorta and femoral vein, found that the cardiac output was increased by the exact amount of blood passing through the artificial arteriovenous anastomosis (at least in small fistulas, that is, fistulas bypassing less than 50 per cent of the cardiac output). The increase in blood volume in chronic arteriovenous anastomosis (Epstein and Ferguson[7]) is only an increase of the plasma volume (T 1824 space) while the P-32 space (red cell volume) remains unmodified.

Ferguson[8] showed that no drop in blood pressure accompanies the creation of a shunt between a vein and an artery; this finding is not accepted by most workers (Holman,[13] Van Loo and Heringman,[28] and Coleridge and Linden[3]). It is generally agreed now that, while there is a marked increase of the local venous pressure close to the anastomosis, the central venous pressure or pressure in the right auricle remains unaltered (Niekerson and associates[22] and Jonnart and associates[18]). The increase in cardiac output and in stroke volume after opening an arteriovenous anastomosis is, according to Shumacker,[26] and others,[18] explained by Starling's law.

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**Fellow of the National Foundation for Infantile Paralysis, 1955-1956.
†Traumatic type of arteriovenous anastomosis, generally caused in those times by the ritual venesection.

Yet, if most of the general cardiocirculatory manifestations of this interesting problem have been thoroughly quantitated and given a satisfactory explanation, very few papers give an adequate evaluation of the blood flow beyond an experimental arteriovenous anastomosis in the affected limb.

Cutaneous thermometry will only yield data on the skin compartment. Deterling, Essex, and Waugh,[5] using a calorimetric method, showed that a lumbar sympathectomy would increase the skin temperature in a normal limb as well as in the extremity chronically affected by an arteriovenous anastomosis. Deep muscular thermometry, thought by Engel[6] to be an accurate index of muscular blood flow, has been proved by Kwok-Kew Cheng[19] to give unreliable figures, as it is a function of both muscle metabolism and blood circulation.

Digital plethysmography, as described by Burch[2] and used by Creech, DeBakey, and Culotta[4] to evaluate the results of aortic and large vessel grafting procedures, gives more sensitive measurements than cutaneous thermometry but has the same limitations. Whole limb venous occlusion plethysmography is inconvenient in the case of chronic arteriovenous anastomosis because of the large venous pool encountered in such lesions. Gregg and co-workers[11] showed indeed that a venous occlusion method is liable to underestimate values of blood flow when compared with a rotameter or an orifice meter method. Those latter procedures, on the other hand, are inadequate when one deals with the existence of large and innumerable collaterals as in the case of chronic arteriovenous anastomoses, which are, according to Reid,[24] "The greatest stimulus to collateral circulation," and to quote Holman,[12] "All avenues of approach to the fistula open to appease, as it were, the thirst of the fistula."

Lewis,[20] using the Stewart calorimeter and sphygmomanometry, showed an increase in circulation beyond long-standing shunts in 3 patients.

Arteriography and oxygen content of the venous blood are useful diagnostic adjuncts but are of little value in a quantitative evaluation of the circulation. In the same way, the reactive hyperemia test of Moskowicz-Matas, the Henle-Coenen phenomenon, and the fluorescein wheal test constitute only handy methods of determining the adequacy of the collateral circulation when one is confronted with the delicate problem of having eventually to sacrifice the main arterial pathway, as in large aneurysms or in extensive congenital cirsoid lesions.

METHOD

Having experimented with the intra-arterial dye-dilution method (with the adjunct of radioactive tracer and external gamma-ray counting setup) in a previous study,[23] we planned the present experiment in order to determine the effects of femoral arteriovenous anastomosis (AVA) on the blood flow beyond the shunt, in both bone and muscle compartments.

Sixteen healthy mongrel dogs, weighing 6 to 22 Kg., were anesthetized with intravenous sodium Nembutal, 30 mg. per kilogram, and submitted to a surgical procedure consisting of a laterolateral anastomosis of the femoral vessels in the groin, right below the emergence of the deep femorals. Eight animals underwent a unilateral femoral shunt while 8 others were submitted to a bilateral

operation (Table I). The size of the communication ranged from 2 to 22 mm. in length (Table II). No heparin was used. The suture material was a 6-0 Ethicon braided silk and Atraumatic welded-on needle.

TABLE I. UNILATERAL ARTERIOVENOUS ANASTOMOSIS

DOG	SIZE OF AVA	TIME AFTER SURGERY	BLOOD TURNOVER RATE (MIN.$^{-1}$) SITE OF AVA TIBIA	SITE OF AVA THIGH	CONTROL TIBIA	CONTROL THIGH	AVA/CONTROL RATIO IN TIBIAS
1	large	1 hr.	0.0	T*	2.1	1.7	0.00
2	large	1 hr.	0.0	T	0.6	-	0.00
3	4 mm.	1 hr.	1.6	0.9	2.1	-	0.76
4	small	1 hr.	1.7	0.8	2.1	2.2	0.81
		1 hr.	-	0.4	-	-	
5	9 mm.	1 hr.	0.0	T	2.3	2.2	0.00
		5.5 wk.	1.8	T	1.8	2.5	1.00
6	16 mm.	1 hr. a.†	0.0	-	0.3	-	
		1 hr. b.	0.0	-	1.2	-	0.00
		1 hr. c.	1.7	-	-	-	
		1 wk.	0.6	-	1.2	-	0.50
7	large	2.5 wk.	1.8	1.5	1.3	1.3	1.40
8	15 mm.	4 mo.	1.0	-	1.7	2.2	0.63
		4 mo.	1.0	-	1.5	-	
		6 mo.	2.3	-	2.7	-	0.90
		6 mo.	2.3	-	2.4	-	

*T indicates turbulence, making quantitative measure impossible.

†a. Femoral artery on control side clamped; b., clamp released; c., femoral vein clamped proximal to AVA (arteriovenous anastomosis).

TABLE II. BILATERAL ARTERIOVENOUS ANASTOMOSIS

DOG	TIME ATTER SURGERY	RIGHT SIZE OF AVA	RIGHT TURNOVER RATE (MIN.$^{-1}$) TIBIA	RIGHT TURNOVER RATE (MIN.$^{-1}$) THIGH	LEFT SIZE OF AVA	LEFT TURNOVER RATE (MIN.$^{-1}$) TIBIA	LEFT TURNOVER RATE (MIN.$^{-1}$) THIGH
9	1 hr.	large	0.1	T*	Crossed anasto-mosis†	1.0	0.2
10	1 hr.	10 mm.	0.7	T	7 mm.	0.0	T
11	1 hr.	small	0.9	0.9	large	0.7	T
	7.5 wk.		2.2	-		0.5	-
	7.5 wk.		1.9	-		0.6	-
12	1 hr.	5 mm.	0.6	T	17 mm.	1.9	T
	6 wk.		0.0	-		2.1	-
13	1 hr.	6 mm.	1.0	-	2 mm.	2.0	-
	1 wk.		1.7	-		2.1	-
	6.5 wk.		2.4	-		2.9	-
14	1 hr.	12 mm.	0.7	T	2.5 mm.	1.5	1.2
15	1 hr.	22 mm.	0.1	T	2.5 mm.	2.3	1.6
	2.5 wk.		0.9	T		2.3	2.4
16	3.5 wk.	3 mm.	0.7	-	11 mm.	1.3	-
			-	-	-	1.2	-

*T indicates turbulance.

†Crossed anastomosis: end-to-end between proximal artery and distal vein and between proximal vein and distal artery.

Usually 2 bulldog clamps were enough to secure perfect hemostasis over a segment of 3 to 6 cm. of artery and vein, while also conveniently approximating both vessels (Fig. 1). A longitudinal incision was made in the artery and in the vein and only one over-and-over 6-0 silk was run, first posteriorly, then anteriorly around the common orifice, so that the back row would be inverting and the front one everting (Fig. 2).

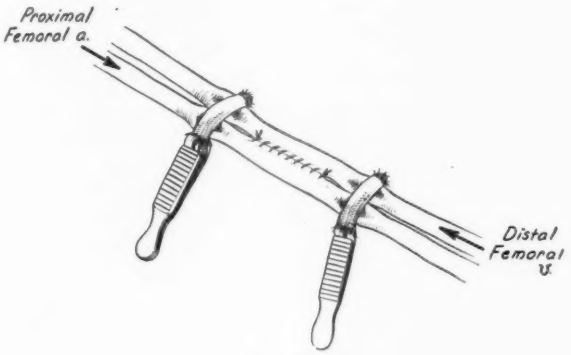

Fig. 1.

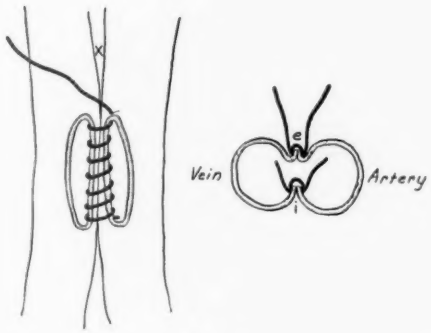

Fig. 2.

Fig. 1.—The bulldog clamps are placed so that a laterolateral anastomosis of the femoral vessels can be performed.

Fig. 2.—On the left is a partly sutured anastomosis. On the right, a cross-section view, showing the anterior everting stitch (*e*) and the posterior inverting (*i*).

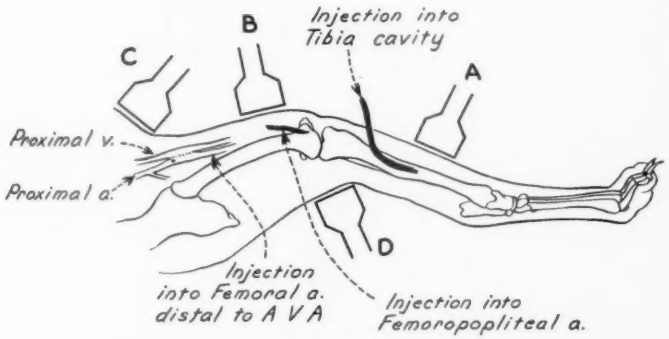

Fig. 3.—When the injection is made into the tibia cavity for blood flow values through bone, the counter is at *A*, usually at the union of the 2 distal thirds of the bone. Occasionally a second counter is at *B*, over the mid-thigh, to detect the time of venous return between *A* and *B*. *B* is the usual location of the counter when one wants to obtain muscle blood flow values, the injection being into the femoral artery, between AVA (arteriovenous anastomosis) and *B*. *B* and *D* are detector positions when the injection is made into the femoropopliteal artery, to determine whether the arterial flow is going up or down the limb. The same is true for counters *B* and *C* in case of turbulence at the site of the AVA.

Sixteen animals were subsequently measured for radioactivity over thighs (muscular mass mostly) and tibias, while being injected, respectively, in the femoral artery (or vein) and in the diaphysis of the tibia (Fig. 3) with a tracer amount of I^{131}-tagged rose bengal (usually 5 to 15 microcuries of I^{131} in 0.25 c.c. of dye).

Twelve dogs (Nos. 1-5 and 9-15) were measured the same day, shortly after the surgical procedure. Ten dogs (Nos. 6-8 and 10-16) were measured between one week and 6 months after the surgery. Dog No. 9 (Table II), besides having

on the right side a "large" femoral arteriovenous anastomosis, that is, 6 mm. long or more, was subjected on the left side to a procedure once hoped by Szilagyi[27] to be corrective for obliterative arterial disease of the extremities, that is, an end-to-end anastomosis between the proximal section of the femoral artery and the distal section of the femoral vein, and vice versa.

To summarize briefly the theory of dilution of radioactive dyes injected in the circulation and its application to the measurement of blood flow, let us remember what follows: (1) After a quick, quasi-instantaneous injection of a tracer dose (usually from 5 to 15 microcuries) of I^{131} in chemical combination with rose bengal, into the femoral artery at the groin, the concentration of dye in the thigh (which is mostly composed of muscular tissue) will be monitored by an external scintillation counter for gamma rays (Nuclear 1620, Chicago) placed over the thigh (Fig. 3, counter B). (2) The concentration curve of activity (1,000 counts per minute) versus time (in seconds), recorded on an Esterline Angus milliammeter, shows, after an initial sharp rise, an exponential decrease during the first 30 to 50 seconds after the injection (Fig. 4, *A*). (3) The transposition of this dilution curve on semilogarithmic paper is a straight line (Fig. 4, *B*). (4) The slope of it, identified as the turnover rate, offers a way to quantitate the circulation through the muscular tissue of the thigh. (5) The same theory applies to an injection of I^{131} rose bengal into the diaphyseal cavity of a bone, through a small polythene catheter inserted into it (Fig. 3, counter A).

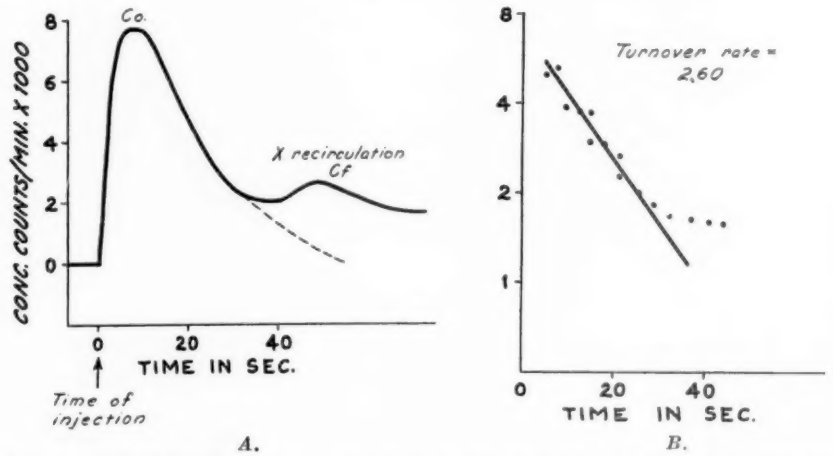

Fig. 4.—*A*, A dilution curve showing rapid rise of activity after injection and exponential fall-off. The second peak represents recirculation. *B*, Downslope of *A* plotted on semilogarithmic paper. Turnover rate is the slope of the straight-line portion.

Usually only one counter was used at the time. For animals Nos. 14 and 15, 2 counters were simultaneously in use (Fig. 3, counters A and B, respectively, over tibia and over mid-thigh) to obtain a value of the venous return time from the tibia to the thigh after injecting the tibia. Occasionally (Dogs Nos. 14 and 15) in order to determine the direction of the circulation after injection into the femoropopliteal artery, 2 counters were used simultaneously above and below the injection site (Fig. 3, counters B and D).

During the very first experiments, the counter was placed at *C* (Fig. 3), that is, over the right iliac region proximally to the fistula, as turbulence effects in the area of the shunt prevented any radioactivity from being detected distal to the arteriovenous anastomosis. This turbulence occurred mostly in the large fistulas, although the 4 mm. arteriovenous anastomosis of Dog No. 4 was enough to cause a marked rushing movement of the blood proximally.

RESULTS

Table I presents the blood turnover rates in tibia and thigh of dogs that had unilateral femoral arteriovenous anastomosis (AVA). Data on animals with bilateral AVA are compiled in Table II.

Where both were measurable, corresponding thigh and tibial turnover rates were mostly about the same, as in our previous study on the effect of sympathectomy.[23] The mean blood turnover rate (with standard deviation) in the control limb one hour after AVA was 1.7 ± 0.4 per minute for tibia (compared with 1.5 in the control tibia after sympathectomy). Muscle (thigh) values were unreliable in limbs with AVA because tracer injected into the femoral artery near the large shunt was subject to turbulence and reverse flow. However, the tibial dilution curves were quite satisfactory (Fig. 5).

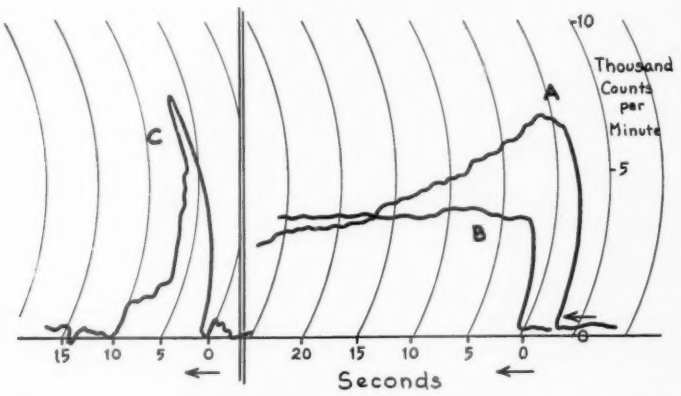

Fig. 5.—*A*, Normal dilution curve in muscle or bone (read from right to left). Turnover rate = 2.30. *B*, Curve in bone where turnover rate equals 0; practically no blood circulates. *C*, Turbulence effect.

About one hour after anastomosis, flow distal to the AVA was in all cases less than in the control side. In general, the larger the AVA, the less the flow distal to it. This relationship is shown in Fig. 6. Flow distal to AVA generally increases with time, approaching normal values 8 weeks after operation (Fig. 7).

One experiment is of particular interest. When the control femoral artery of Dog. No. 6 was clamped, the tibial blood turnover rate dropped to 0.3 but not to 0, indicating the extent of normal collateral circulation. When the clamp was taken off, turnover rate jumped to 1.2 per minute. On the side of the 16 mm. AVA, tibial turnover rate was 0 until the femoral vein was clamped proximal to the AVA; with this, it rose to 1.7 per minute.

The most aberrant result was that of Dog No. 12, in which there was consistently more flow on the left tibia, despite a larger AVA in that limb (17

mm. as compared to 5 mm. on the right); the presence of the larger shunt on the left was confirmed by a stronger thrill, more edematous limb, and marked bradycardia on pressure over the AVA (Branham-Nicoladoni sign). Possibly some vascular anomaly was present. In Dog No. 2 there was an abnormally low turnover rate (0.6 per minute) in the control tibia, which also remains unexplained. Only one animal (No. 11 with bilateral AVA) had a slight decrease in flow in one tibia, after a lapse of several weeks, while the turnover rate in the opposite tibia more than doubled.

In order to evaluate the reproducibility of the technique, several measurements were repeated, under exactly the same conditions, 15 minutes after the first measurement. These are collected in Table III. Four measurements were made of tibia-to-thigh transit times, using 2 detectors simultaneously. These transit times should be inversely correlated with turnover rate, and they are (Table IV). Several of these animals were eventually sacrificed. In each case the AVA was patent and the same size as estimated at operation.

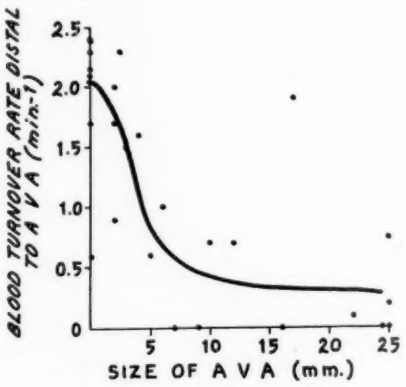

Fig. 6.

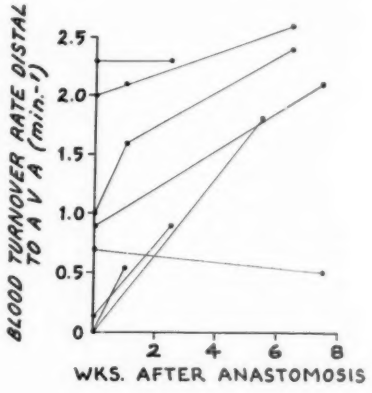

Fig. 7.

Fig. 6.—Relation between size of fistula and flow distal to it.
Fig. 7.—Relation between flow distal to fistula and time after creation of fistula.

TABLE III. REPRODUCIBILITY OF MEASUREMENT

DOG	TURNOVER RATE (MIN.$^{-1}$)	
	1	2
2	0.3	0.2
8	1.0	1.0
11	0.7	0.8
13	2.4	2.9
16	1.3	1.2

Fifteen minutes elapsed between runs 1 and 2.

TABLE IV. TIME OF VENOUS RETURN FROM TIBIA TO THIGH (ACUTE MEASUREMENTS IN DOGS NOS. 14 AND 15)

DOG	SIDE	SIZE OF FISTULA (MM.)	BLOOD TURNOVER RATE IN TIBIA (PER MM.)	TIME TIBIA TO THIGH (SECONDS)
14	left	2.5	1.53	15
14	right	12.0	0.70	60
15	left	2.5	2.26	11
15	right	22.0	0.14	no return

DISCUSSION

That blood flow distal to an AVA should be diminished in proportion to the size of the shunt is quite consistent with fluid dynamics. Blood, like electricity, takes the path of least resistance. The resistance of the AVA apparently does not change with time; therefore, if distal flow is to increase, either the effective resistance of the distal vascular channels must be decreased or the total limb flow through both AVA and distal channels must go up. Voluminous evidence has accumulated previously that both mechanisms are used: (1) opening of collaterals reduces the peripheral resistance; and (2) the cardiac output is increased by at least as much as flows through the shunt.

As cardiac output goes up instantaneously with creation of an AVA,[9] the gradual increase in flow distally over the next few weeks must be accounted for by the gradual opening of collateral channels. Holman[14, 15] has meticulously studied the conditions at the fistula itself which influence this development. We found a similar effect after lumbar sympathectomy.[23] Turnover rates in thigh and tibia immediately went up 20 per cent over the control limb; several weeks later they had risen 70 per cent.

It is of some importance for surgeons to know how long it takes for optimal collateral circulation to develop, since this may influence the choice of the time to operate upon an arteriovenous fistula. The danger of congestive failure is, of course, minimized by immediate closure of the fistula, and, if the artery can be repaired at this time, circulation to the distal limb is restored at once. In cases in which it becomes necessary to sacrifice the artery, results might be better if operation were postponed several weeks until collaterals were well developed. Some have thought that collaterals do not develop unless the fistula is closed, either by operation or external pressure, but our results contradict that thesis.

Studies on animals cannot, of course, be directly applied to humans without making similar measurements on patients, and this we plan to do. It would be of particular interest to compare traumatic and congenital arteriovenous fistulas, since the latter probably represent multiple abnormal arteriovenous communications, as reflected in more rapid bone growth and so forth, and therefore may have greatly increased turnover rates in the distal extremity.

SUMMARY

Using a radioactive dye (I^{131} rose bengal) and an external gamma-ray detection system, we have measured the blood turnover rates in thigh and tibia of dogs with femoral arteriovenous anastomosis (AVA). In control (unoperated) limbs, turnover rates in tibia and thigh were very nearly the same. In limbs with AVA, thigh measurements were unreliable because of turbulence and reverse flow in the femoral artery, where the tracer was injected. In the tibia, blood turnover rate was reduced; the larger the AVA, the less tibial blood flow. Over a period of several weeks after operation, tibial flow tended to return to normal, presumably due to development of collateral circulation.

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AN EXPERIMENTAL STUDY OF THE EFFECT OF MECHANICALLY INDUCED ISCHEMIA UPON THE MAMMARY CORONARY ANASTOMOSES

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IT is now recognized that in the Western Hemisphere death by coronary vascular occlusion has become one of the major medical problems which require solution. For this reason a great many approaches to the subject are being explored in all the fields of medicine. In this paper it is proposed to discuss our experience with one aspect of this vast subject and to present the results of an experiment which was carried out in order to ascertain whether or not it is possible to induce myocardial ischemia with a mechanical device, and if so, to see the effect of this ischemia upon the proportion of successful "anastomoses" between an internal mammary artery simultaneously implanted into the myocardium of the left ventricle and the vascular bed of that ventricle.

It is beyond the scope of this article to discuss the many experimental operations for the relief of myocardial ischemia which have been devised since the literature on this subject is well known and the results of experimental procedures appear to be quite variable.

It appears that the majority of the experimental work which has been done is subject to one major criticism. The operation for relief of the condition has been performed before the condition itself has been developed. It is obvious that this is a completely unrealistic situation. In a large proportion of the experiments reported, the test for the efficacy of an operation for myocardial ischemia, performed on a hitherto normal heart, has been to ligate one or more of the major vessels which supply the various parts of the left ventricle. A suitable term for this approach is not revascularization, but supervascularization.

This approach has many merits and the results of some of the experiments have been very encouraging; however, it is our opinion that vascularization procedures have not been given a really fair chance to show their value, since a normal myocardium has all the blood supply that it requires and will be less inclined to accept new vessels than a myocardium which is already deprived of its requirements, and where the demand for blood exceeds the supply.

For this reason attempts have been made to produce ischemia in the hitherto normal myocardium by metabolic means and mechanical devices. We selected a mechanical method for this short-term experiment.

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Several lines of investigation in this direction have been pursued, the most notable being (1) injection of microspheres into the coronary ostia, (2) a slowly occluding thumbscrew type of clamp, (3) a spring clip held open by absorbable catgut, the spring of which closed as the catgut which held its jaws open was absorbed, and (4) the direct application of fibrogenic material to the vessel wall. The first and third methods were unpredictable in their efficacy, however, and the tightening of the screw in the second procedure produced a sporadic rather than gradual constriction and required multiple operative procedures.

During the past 5 years a slower and more evenly progressive method of producing coronary arterial constriction has been sought in this center. The use of fibrogenic substance was favored and for a period of time we carried out experiments with cellophane wrapping and perivascular injection of dicetyl phosphate dissolved in toluene around the 2 main branches of the left main coronary artery. Neither of these procedures proved adequate and for several months the problem was unsolved.

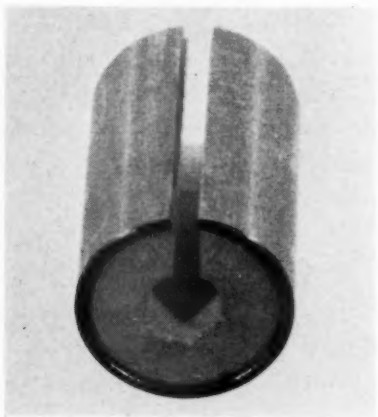

Fig. 1.—Photograph of Ameroid device.

Berman[2] designed a device which consisted of a stainless steel jacket containing a cylinder of hygroscopic plastic called Ameroid. A slit was made in the jacket and plastic so that the device could be slipped over a vessel and allowed to remain in place (Fig. 1). The plastic gradually absorbed fluid, expanded centripetally, and compressed the vessel lying within its lumen.

This device gave us considerable inspiration, and an in vitro experiment was performed by Litvak.[3] He showed that the rate of closure of the Ameroid was fairly constant and should be reasonably predictable in vivo. The rate of absorption of plain Ameroid was found to be too rapid for a long-term survival. The plastic was, therefore, coated with various substances in order to slow down the rate of water absorption. The most suitable coating appeared to be melted Vaseline in which the Ameroid was soaked for a period of 30 minutes after sterilization with benzalkonium chloride of strength 1/000.

The Ameroid constrictors were placed on the origins of the anterior descending and circumflex branches of the left coronary artery. The results of

the early series showed that the untreated Ameroid behaved in a stable manner in vivo and would constrict the coronary arteries to a critical level and produce death within 10 to 15 days. The Vaseline-treated Ameroid, however, was less constant in its rate of closure in vivo and the critical level of occlusion would be reached in a period of time which varied from 3 to 28 weeks.

When the critical level of coronary artery constriction was reached, the animals appeared to be quite well, provided they did not exert themselves or become excited. If they became involved in any excitement such as combat or jumping for food, they would suddenly fall down and be dead by the time the custodian reached them.

On autopsy the Ameroids were found to have produced considerable constriction of the coronary vessels (Fig. 2). Furthermore, in the case of the untreated Ameroids, varying degrees of thrombosis occurred within the vascular lumen, and localized peripheral thrombosis with infarction was noted.[3]

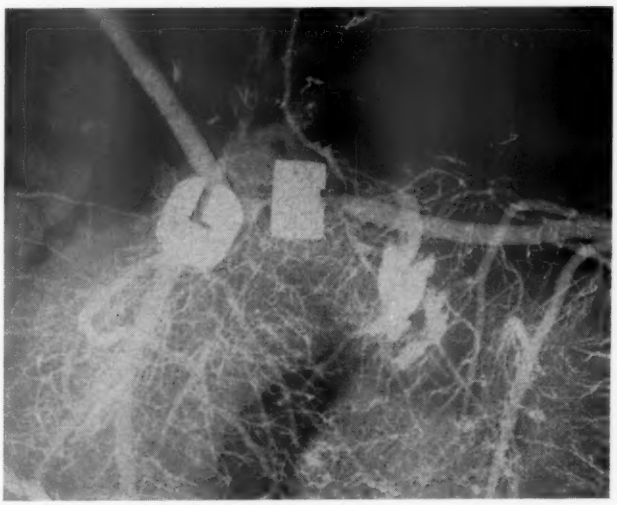

Fig. 2.—Specimen of heart injected with Schlesinger mass through left main coronary artery ostium showing degree of constriction of circumflex branch of left coronary artery produced by Ameroid device after 8 weeks.

This phenomenon appeared to be sufficiently constant to suggest that pressure of an expanding Ameroid would produce enough ischemia to make the demand for blood to the myocardium exceed the supply and thus to resemble the state of affairs present in localized atherosclerosis of the coronary vessels.

With this mechanical device available an experiment was designed to ascertain what proportion of internal mammary arteries implanted into the myocardium would form adequate anastomoses with the vascular system of the left ventricle in which ischemia was being simultaneously produced.

METHODS

Twenty mongrel dogs, weighing between 45 and 55 pounds were selected and coated Ameroids were applied to the main branches of the left coronary artery.

The technique of this procedure was as follows. A thoracotomy was performed through a left fourth or fifth intercostal incision. The ribs were spread with self-retaining retractor and the lungs retracted posteriorly. The pericardium was incised longitudinally from its superior reflection onto the aorta to a point halfway between the base and apex of the left ventricle. This incision may lie anterior or posterior to the phrenic nerve.

The pericardial edges were retracted with self-retaining sutures. The left auricular appendage was then retracted posteriorly and held in position with a self-retaining suture passed through its tip.

This maneuver displays the great cardiac vein turning into the coronary sinus and the aortic-pulmonary sulcus, in the base of which lies the left coronary artery, branching into its 2 main divisions, the circumflex and the left anterior descending coronary arteries.

Fig. 3.

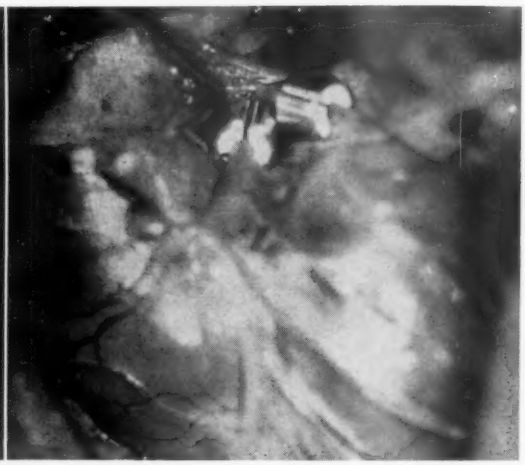

Fig. 4.

Fig. 3.—Photograph taken at operation showing requisite dissection of the branches of the left main coronary artery.

Fig. 4.—Same specimen as Fig. 3, showing Ameroid constrictors in position.

The epicardium was dissected from these vessels and then by both sharp and blunt dissection the vessels were dissected free and mobilized with their branches for a distance of approximately 1 cm. (Fig. 3). Elevation ligatures were passed under each vessel, the vessel was lifted up by gentle traction, and an Ameroid was passed around it (Fig. 4). When this was completed the pericardium was closed with silk and the thoracotomy incision with stainless steel wire. With a little practice this procedure may be performed by a lone operator in about 40 minutes.

There were no operative deaths and these animals were sent out to the farm on the fifth postoperative day. These animals were carefully observed by the farm supervisors and their manner of death recorded.

In order to obtain reassurance that the cause of the animals' death was not merely the presence of a bulky object in a sensitive area, 5 animals were treated with "false" Ameroids which were made identical in size and appearance to the others with the exception that an inert plastic was used instead of hygroscopic Ameroid. None of these animals died and after 7 months they

were sacrificed and inspected. Macroscopic and microscopic examinations revealed minimal perivascular fibrous deposition but no constriction as a result of the presence of the device, whereas those with hygroscopic Ameroids displayed considerable constriction accompanied by endothelial proliferation. Figs. 5 and 6 show transverse sections of a coronary artery before entering and with the Ameroid tunnel. There was no complete occlusion of the coronary vessels amongst any of the 25 true or false devices.

Fig. 5.

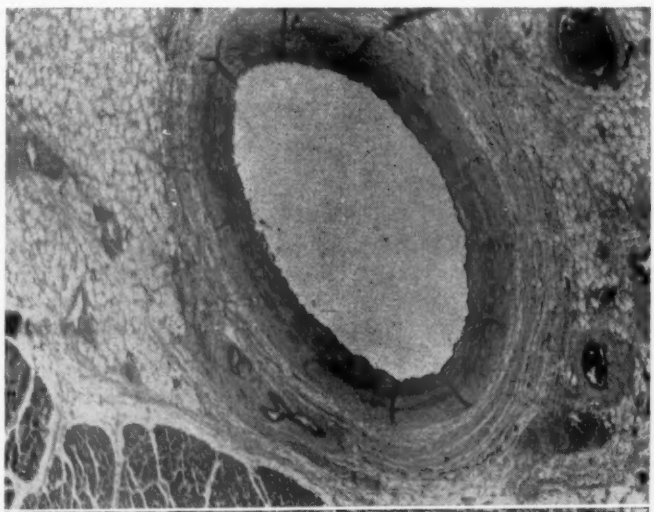

Fig. 6.

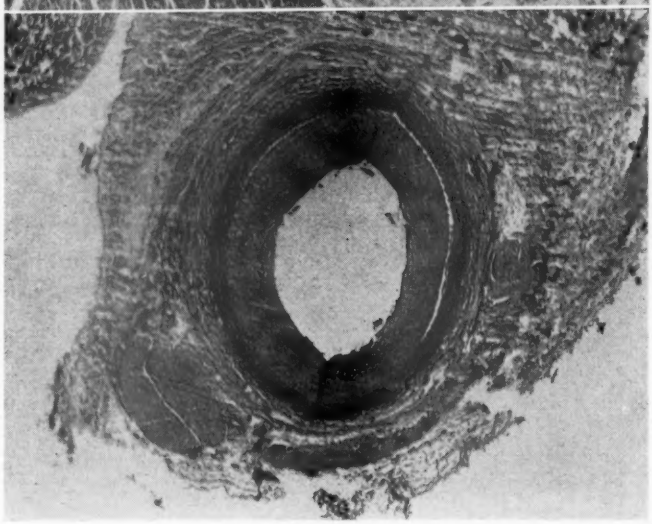

Fig. 5.—Photomicrograph of transverse section of circumflex branch of left main coronary artery just after the bifurcation before entering Ameroid.

Fig. 6.—Continuation of vessel in Fig. 5 on same scale. This section is in center of area constricted by Vaseline-coated Ameroid showing stenosis caused by endothelial proliferation and perivascular fibrosis. The Ameroid has been removed.

Autopsies were performed on all the animals and their left coronary arterial tree was injected with Schlesinger mass at a pressure of 110 mm. Hg and x-ray pictures were taken. In all these cases infarction was minimal or

nonexistent, but the coronary arteries were obviously constricted at the site of the Ameroid application (Fig. 2), and on section the lumen showed local narrowing within the encircled segment (Fig. 6).

Following this series of 25 animals the same procedure was carried out on 20 more, and after the Ameroids were placed in position an internal mammary arterial implantation was performed according to the technique described by Vineberg and Buller,[4] with the following differences. The internal mammary artery was freed to a higher level. Instead of leaving the sixth intercostal artery long, this vessel was cut off flush with the freed internal mammary artery so that a lateral defect was produced before imbedding the artery in the myocardial tunnel.

Fig. 7.—Gross specimen, 3-week implant, injected with Schlesinger mass showing early vascular budding.

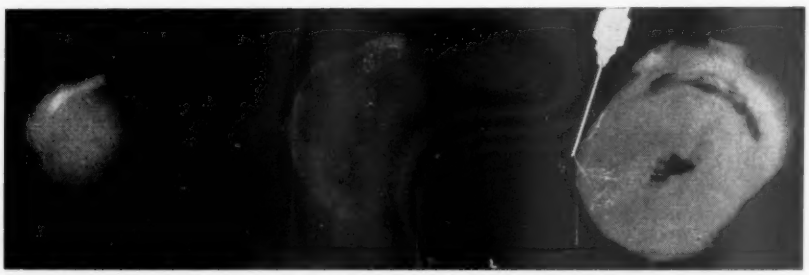

Fig. 8.—Transverse section of 4-week implant injected with Schlesinger mass showing only localized anastomosis in anterior wall of left ventricle.

The pericardium was not closed and the thoracotomy was closed with stainless steel wire sutures. This combined procedure can be performed by a lone operator in about 3 hours.

There were no operative deaths and all 20 animals made an uneventful recovery. One animal succumbed to a pulmonary infection 3 weeks postoperatively. The animals were transferred to the farm after 5 days and observed in the same manner as the control series.

It was hoped that the implanted internal mammary artery would be adequate to take over the blood supply of the left ventricle to such a degree that the animals would not succumb to the effects of Ameroid constriction. This happy situation did not, however, occur and at varying intervals the animals succumbed in a similar manner to the controls. Autopsies were performed and the hearts refrigerated and later injected with Schlesinger mass by the usual technique.

The animals which survived 20 weeks were reoperated upon and the condition of the implants examined. All were patent and pulsating. Those animals were then sacrificed, their hearts removed and, after flushing them out in normal saline, were refrigerated for 48 hours to relieve vascular spasm, in the same manner as those which died on the farm.

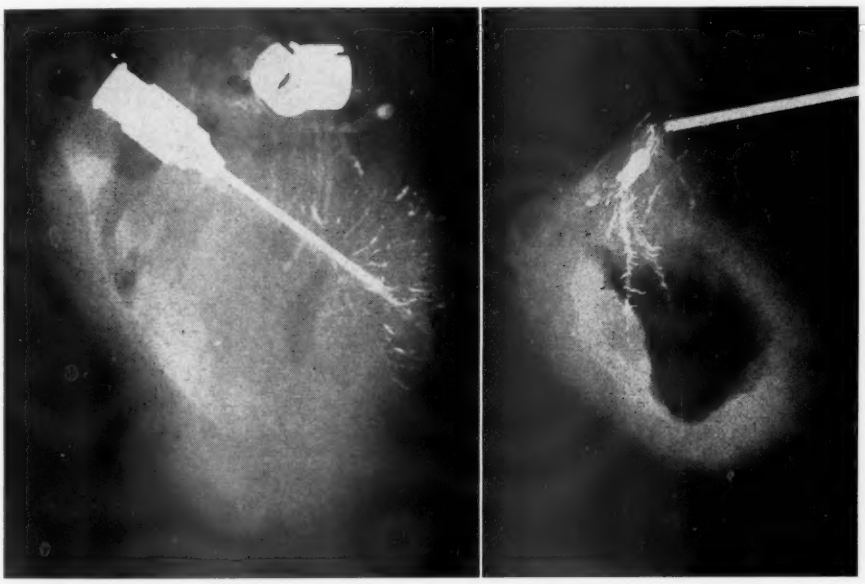

Fig. 9. Fig. 10.

Fig. 9.—Gross specimen, 6-week implant, injected with Schlesinger mass showing early anastomosis with coronary vascular tree.

Fig. 10.—Transverse section of Fig. 9 showing injection limited to anterior portion of left ventricle.

The internal mammary artery was then cannulated and the specimen injected with Schlesinger mass at a pressure of 110 mm. Hg. Roentgenograms were made of the gross specimens (Figs. 7 to 19, inclusive). The hearts were then sectioned transversely and x-rayed again, and the injected myocardial volume was examined.

The term volume is used because we are interested in the amount of myocardium which is affected by total revascularization and not merely by small surface collaterals through which only a small amount of blood will flow and which will be only adequate to supply the muscle mass to a limited depth from the surface.

Initially no correlation was made between the length of time that the animal survived operation and the amount of myocardium which had accepted

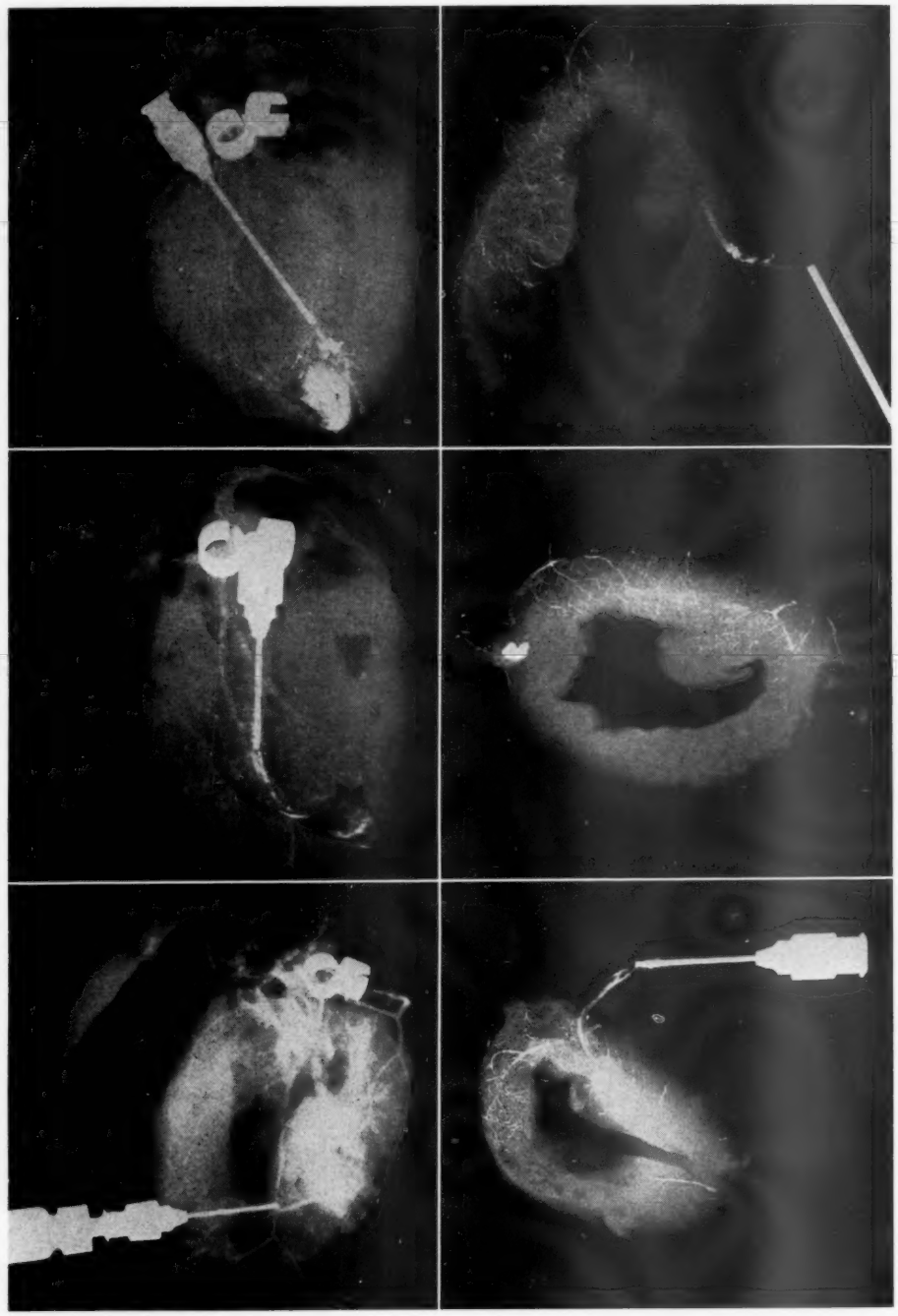

Fig. 11.

Fig. 12.

Fig. 13.

Fig. 14.

Fig. 15.

Fig. 16.

Fig. 11.—Gross specimen, 8-week implant, injected with Schlesinger mass showing wider distribution of dye in vascular system of left ventricle.

Fig. 12.—Transverse section of Fig. 11 showing injection of anterior one-half of left ventricle.

Fig. 13.—Gross specimen, 12-week implant, injected with Schlesinger mass showing good filling of the area supplied by the anterior descending branch of the left coronary artery.

Fig. 14.—Transverse section of Fig. 13 showing filling of anterior part of left ventricle as well as anterior half of interventricular septum and part of right ventricle.

Fig. 15.—Gross specimen of 22-week implant showing good filling of vascular system of left ventricle.

Fig. 16.—Transverse section of Fig. 15 showing filling of anterior two-thirds of left ventricle.

Fig. 17.—Gross specimen of 30-week implant injected with Schlesinger mass showing extensive anastomosis with whole of left ventricle.

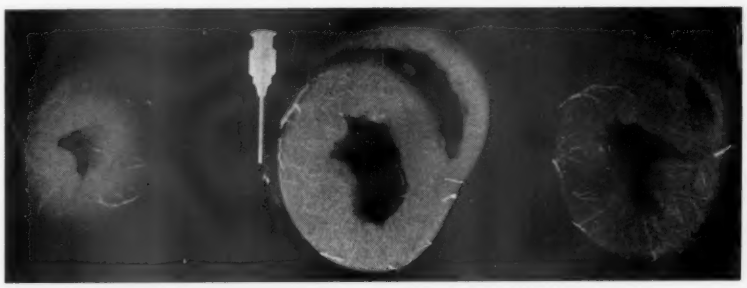

Fig. 18.—Transverse section of Fig. 17 showing filling of most of the left ventricle, part of the right ventricle, and all except the center of the interventricular septum.

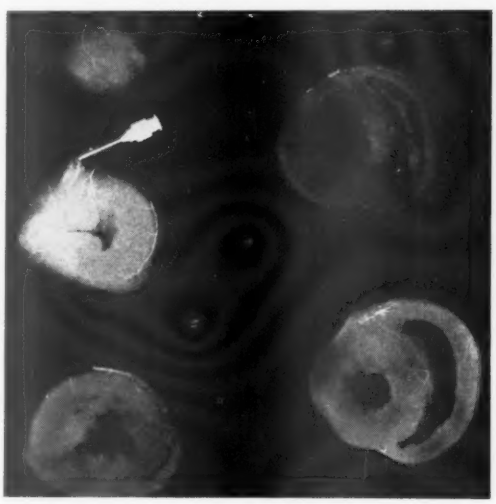

Fig. 19.—Transverse section of 29-week implant injected with Schlesinger mass showing good filling of the left ventricle, anterior one-half of right ventricle, and interventricular septum.

Schlesinger mass. It was, however, encouraging to find that a larger proportion of mammary coronary anastomoses than had been expected according to previous work and that minimal endothelial proliferation on histologic section had occurred in the wall of the implanted vessels and their developing vascular buds (Figs. 20 and 21). The number of successful anastomoses was 17 of 20 (85 per cent).

However, when the series was completed it was obvious that a relation did exist between the time that the implant had been present before death and the volume of myocardium supplied by this extracoronary source. It was observed that the volume of myocardium injected with the Schlesinger mass was smallest in the animals which had suffered an early demise. On the other hand, those which had survived for the longer periods had the greater volumes of myocardium injected and the most obvious arterial budding on microscopic section. The injected area and thus the most profuse anastomotic area commences around the line of implantation and spreads in a centrifugal manner (Figs. 7-19). The last portions to be filled are the posterior part of the base of the interventricular septum and the inferoposterior portion of the left ventricle.

A study of Figs. 7 to 19 shows how the implanted internal mammary artery at the end of 2 to 3 months has formed prolific anastomoses with the vessels of the anterior wall of the left ventricle. When such animals were excited or exercised the coronary arteries narrowed by Ameroid constriction were unable to supply the left ventricle with the increased amount of blood it required. The implanted artery only supplied blood to the region of the left anterior descending coronary artery. These animals died.

However, when sufficient time had elapsed after implantation, 5 months appearing to be the minimum, the entire left ventricle appeared to receive blood from the implanted artery. Such animals could not be killed by exercise or excitement, even though both the anterior descending and circumflex arteries were greatly reduced in diameter at their origin.

This small series has given us cause to preview previous histories of implantations performed with and without attempts to produce ischemia. We have found that those hearts which had been allowed to survive for the longest time before sacrifice or death were those in which the coronary system was filled the most completely with dye or plastic, injected through the implanted internal mammary artery. This is a most important point to realize in the rehabilitation of patients upon whom the operation of implantation has been performed for angina pectoris or coronary thrombosis, for their improvement may seem to be slow initially.

It is likely that in a heart which has disease of the major vessels resulting in a myocardial demand for blood which exceeds the supply another hazard may be present. This hazard is the situation produced when a new and relatively undiseased vessel is introduced into the ischemic myocardium, forms an anastomosis with the coronary system, and supplies well-oxygenated blood to a localized volume of muscle around the line of implantation. This muscle

Fig. 20.

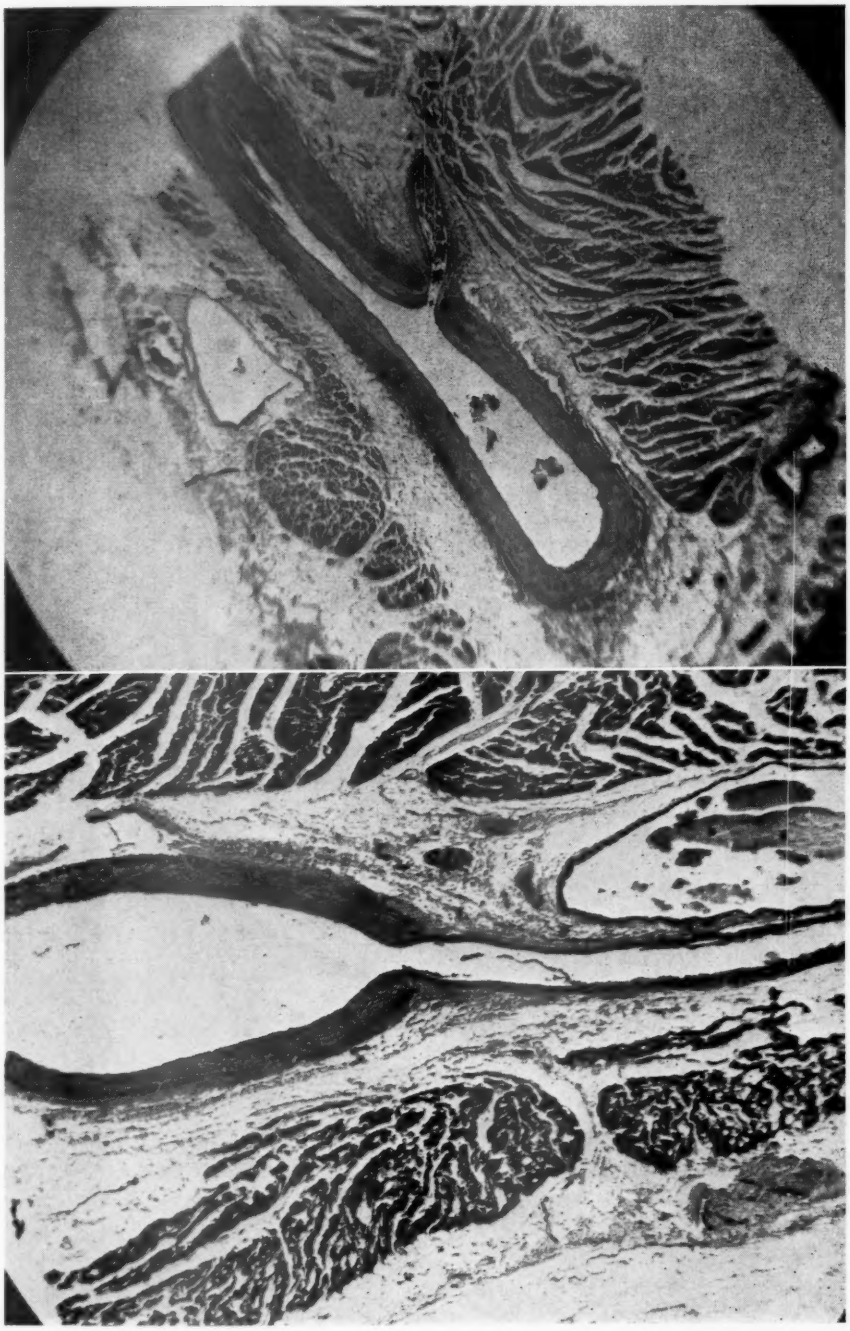

Fig. 21.

Fig. 20.—Photomicrograph of Fig. 7, showing implant sectioned through a vascular bud within the myocardium.

Fig. 21.—Photomicrograph of 29-week implant embedded in myocardium showing minimal change in the arterial wall and the development of a large vascular bud.

will be periodically at a different electrical potential from the muscle which surrounds it. This situation is exactly that described as the "reverse trigger zone" by Beck and associates.[1]

The heart will thus be electrically unstable and, when subjected to the stress, will be susceptible to the hazard of "mechanism failure"[1] and in danger of ventricular fibrillation. This state will endure until the implanted vessel has been present for many months and connections have been established over the whole muscle mass to such a degree that differential oxygenation does not occur.

SUMMARY AND CONCLUSIONS

1. A mechanical method for simulating localized coronary arterial disease has been further investigated and found successful.

2. In this series the proportion of "take" or anastomosis of the implanted internal mammary artery with the vascular system of the myocardium was 85 per cent after ischemia was artificially induced compared to a rate of about 50 per cent in previous series with previous methods.

3. The establishment of vascular collaterals from the implanted artery to the whole myocardium takes many months.

4. Too rapid rehabilitation of a patient after implantation may produce a dangerously unstable myocardium.

We wish to express our gratitude to Paul Roustan of the Department of Experimental Surgery and his staff for their great assistance to us and without whom this experiment would not have been possible and to Frances L. Smith of Pearl River, N. Y., who made the presentation so much more easy.

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AN EVALUATION IN DOGS OF THE RELATIONSHIP OF PULMONARY, BRONCHIAL, AND HILAR ADVENTITIAL CIRCULATION TO THE PROBLEM OF LUNG TRANSPLANTATION

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INTRODUCTION

IT has been known for a long time that the lung has a dual blood circulation.[5, 10, 12] The precise role of the pulmonary artery blood flow and that of the bronchial arteries and the hilar adventitial arteries, however, is in some respects unclear. For example, the degree to which the lung depends for its nutrition upon pulmonary artery blood or bronchial artery blood is uncertain. Recent surgical developments lend increased importance to this question. One of these developments may be cited as follows: in lung transplantation, failure of the homologous transplant often is ascribed to immunologic resistance on the part of the recipient. However, the duality of the lung circulation raises a question as to the role of the bronchial and hilar adventitial circulation with respect to the success of lung transplantation. If the systemic flow to the lungs is indispensable to normal lung function, then successful lung transplantation would depend upon integrity of this flow as well as upon solution of the immunologic problem. In order to obtain more knowledge about the sensitivity of the lung to temporary and permanent interruption of the pulmonary and systemic lung blood flow, several experiments were performed.

METHOD

Dogs were anesthetized with Nembutal or ether and operated upon with sterile precautions and with the use of positive pressure endotracheal respiration. Penicillin and streptomycin were administered in the postoperative period. Survival data were obtained, and blood gas analyses were determined with regard to oxygen and carbon dioxide content of the pulmonary artery and pulmonary vein blood. Lung biopsies were made after removal of occluding clamps, and the animals which succumbed were autopsied.

Experiment One.—The left pulmonary artery was exposed through the left chest and occluded for one hour. Several days later the right lung was removed through a right thoracotomy.

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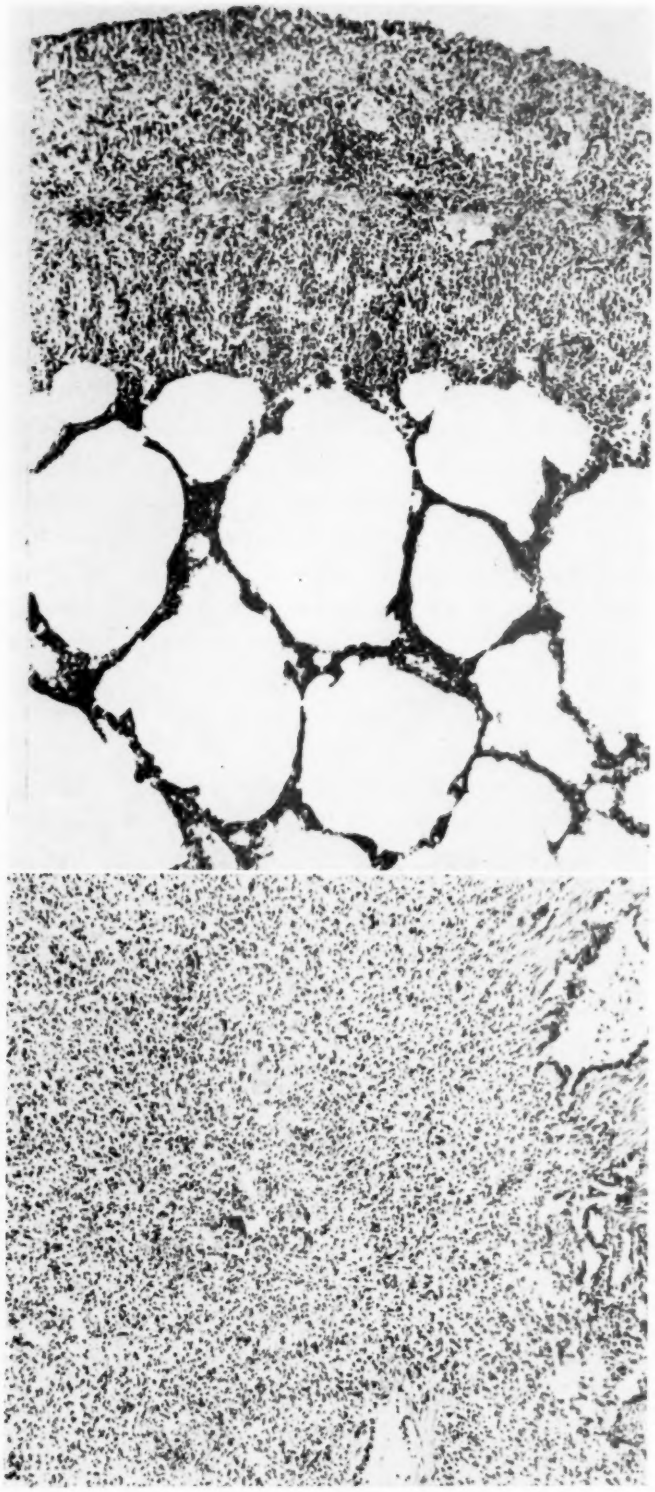
A.



B.

Fig. 1.—This shows the right pulmonary artery occluded by a clamp and the intercostal arteries occluded where they arise from the aorta.

Experiment Two.—The left pulmonary artery was approached through the left chest and occluded for 15 minutes. In addition, the bronchial arteries to the left lung and the hilar adventitial arteries were divided and tied. A few days later the right lung was removed through a right thoracotomy.

Experiment Three.—This protocol was similar to that in experiment two except that the left pulmonary artery occlusion was for one hour. Blood gas analyses for oxygen and carbon dioxide content were made upon blood drawn from the pulmonary artery and left pulmonary veins just before and a few minutes after the period of occlusion.

Experiment Four.—The right pulmonary artery was occluded after gaining access to the mediastinum through the left chest, and the bronchoesophageal arteries were occluded by bulldog clamps applied near the origin of these vessels from the aorta (Fig 1). After 15 minutes of occlusion of these arteries, which thus occluded the right pulmonary artery and the bronchial artery supply to each lung, the left lung was removed.

Experiment Five.—After gaining access to the right pulmonary artery and the bronchoesophageal arteries through the left chest, the right pulmonary artery and the bronchial arteries were occluded for 30 minutes. Left pneumonectomy was performed immediately after release of the occluding clamps.

Experiment Six.—The bronchial arteries to the right lung and their mediastinal connections were divided after gaining access through a left thoracotomy. Immediately after division of these vessels a left pneumonectomy was performed.

RESULTS

The survival data are summarized in Table I. It can be seen that in experiment one, 3 of 3 animals subjected to occlusion of the left pulmonary artery for one hour survived contralateral pneumonectomy. Their behavior after removal of the right lung was essentially normal by gross observation.

TABLE I. SURVIVAL AFTER CONTRALATERAL PNEUMONECTOMY

EXPERIMENTS	NUMBER OF ANIMALS	SURVIVALS
1. Occlusion pulmonary artery—1 hour	3	3
2. Occlusion pulmonary artery—15 min., division bronchial artery	7	2
3. Occlusion pulmonary artery—1 hour, division bronchial artery	9	1
4. Occlusion pulmonary artery and bronchial arteries—15 min.	6	5
5. Occlusion pulmonary artery—30 min.—and bronchial artery	5	4
6. Division bronchial artery only	7	2

In experiment two, in which the pulmonary artery to one lung and the ipsilateral bronchial and hilar adventitial arteries were divided, 2 of 7 dogs survived subsequent contralateral pneumonectomy. The usual course of events was death of the animal within 24 to 48 hours after the contralateral

pneumonectomy. At the time of the contralateral pneumonectomy it was noticed that the lung which had been subjected to pulmonary artery occlusion and bronchial and hilar adventitial artery division appeared viable. However, the lung did not ventilate but rather was motionless, heavy appearing, and pallid. In a few cases the bronchus was opened and no gross lesion was found. Microscopic studies of the lung at this time showed a moderate amount of pleural reaction but no significant other lesion, except for some slight interstitial infiltrate (Fig. 2, *A*). At the time of death of the animals 24 to 48 hours later the remaining lung now was heavy, red, wet, and quite solid. The microscopic appearance at this time was one of atelectasis, increased intra-alveolar fluid, and interstitial infiltrate (Fig. 2, *B*).

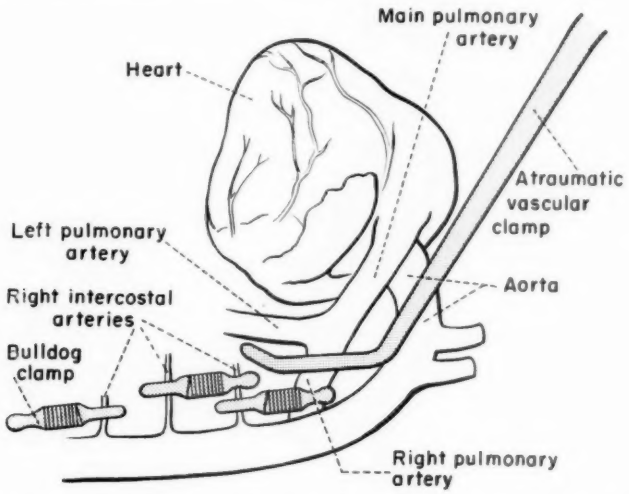


Fig. 2.—*A*, Pleural reaction at the time of contralateral pneumonectomy (E810). *B*, Marked atelectasis the day after contralateral pneumonectomy (E810).

In experiment three, in which the pulmonary artery to one lung was occluded for one hour and the ipsilateral bronchial and hilar adventitial arteries divided, only one of 9 dogs survived contralateral pneumonectomy. In this set of animals observations were made upon the oxygen and carbon dioxide content of the pulmonary artery and the left pulmonary veins just before and just after the period of occlusion. It can be seen from the data in Table II that there was no significant change in these values at this time.

TABLE II

DOG	CARBON DIOXIDE VOLUME (PER CENT)		OXYGEN VOLUME (PER CENT)
E808	before	51.53	15.80
	after	48.55	16.79
E811	before	51.95	20.40
	after	51.75	20.67
E812	before	27.84	20.49
	after	54.05	21.26
E813	before	56.76	15.19
	after	47.70	15.39

The above data were obtained on blood samples from the left pulmonary veins drawn just before and after 60 minutes of pulmonary artery occlusion and complete interruption of the bronchial and adventitial arteries.

Again, the appearance of the left lung, after the occlusion and prior to the pneumonectomy, was similar to that described in experiment two. The remaining lung at autopsy again presented the striking picture of congestion and atelectasis described in experiment two. The time of death usually was within 48 hours of the contralateral pneumonectomy.

Temporary occlusion of the right pulmonary artery and the bronchial arteries for a period of 15 minutes, as in experiment four, was well tolerated. It can be seen that 5 of 6 animals subjected to this procedure survived the contralateral pneumonectomy. When the period of temporary occlusion was for 30 minutes, as in experiment five, 4 of 5 animals survived contralateral pneumonectomy.

In experiment six, in which the bronchial arteries and the hilar adventitial arteries were extensively divided, only 2 of 7 dogs survived the contralateral pneumonectomy. The usual course of events was failure to survive more than 48 hours after the pneumonectomy. The remaining lung at the time of death of the animal presented the appearance of hemorrhage and atelectasis previously described.

DISCUSSION

Brock[3] showed that unilateral pulmonary artery ligation without removal of the affected lung could be carried out in man, permitting a 2-stage pneumonectomy. In the experimental animal, pulmonary artery ligation was followed by some atelectasis and fibrosis on the ligated side, but necrosis did not occur.[11] Davis[4] showed that the monkey lung tolerated unilateral pulmonary artery occlusion up to 48 hours with little histologic change of a permanent nature. Blades[1] found that occlusion of the hilar structures by an occluding tourniquet was poorly tolerated in that subsequent contralateral pneumonectomy was followed by death in most of the animals.

In experiments herein reported in which dogs were subjected to left pulmonary artery occlusion for one hour contralateral pneumonectomy was well tolerated. Three of 3 animals subjected to this procedure survived without ill effect. One might infer from this either that the pulmonary artery flow is not essential to the maintenance of lung function and survival in the dog or that the safe time limit of occlusion is in excess of one hour. It hardly seems necessary to labor the point that flow through the pulmonary artery ordinarily is a condition of survival. However, it did seem to suggest that further investigation of the arterial supply of the lung was warranted.

Karsner and Ash[7] had noted that there was no gross anatomic change after ligating and dividing the bronchial arteries. Ellis[6] found damage to the central portion of the bronchi after injecting the bronchial arteries with plastics. In experiment two, three, and six, the bronchial arteries were carefully divided along with the remaining adventitial hilar vessels. At this point the findings were in agreement with those of Karsner and Ash. Observations of lungs subjected to this maneuver showed that the lung, while appearing viable, did not ventilate with respiration. The striking thing about these

experiments, however, was the high mortality when contralateral pneumonectomy was performed after division of the bronchial and hilar adventitial arteries. The lung was found at autopsy to be heavy, wet, hemorrhagic, and obviously incapable of supporting life. Apparently, contralateral pneumonectomy is a more sensitive criterion of the effect of alteration of pulmonary circulation than is the gross appearance.

When the bronchial arteries were identified at their origin from the aorta and temporarily occluded with bulldog clamps, the above findings were not noted. These animals were able to survive contralateral pneumonectomy rather regularly. It is true that the remaining hilar adventitial vessels were not dissected out and divided in these latter cases, so it is quite possible that enough blood made its way through these potential collateral channels to support functional integrity of the lung. However, it was thought that this procedure of using bulldog clamps on these vessels avoided the possibility of permanent crushing injury to the bronchial vessels and the adventitial vessels of the hilum. It is necessary to point out that conclusive proof of only temporary bronchial artery interruption was not obtained by these experiments. However, gross inspection of the vessels after release of the bulldog clamps seemed to indicate that flow had returned through these small arteries. In any case, it would seem worth noting that the result of detailed and complete interruption of the bronchial and adventitial arteries was analogous to the result obtained by Blades[1] when temporary occlusion was carried out with a hilar tourniquet. When the vessels were occluded with bulldog clamps, either the occlusion was temporary and within the safe time limit of occlusion or enough collateral was maintained through the rest of the adventitial vessels to nourish the lung adequately. Further evidence of the importance of the bronchial and adventitial circulation is found in the results of experiment six. Only 2 of 7 dogs subjected to extensive division of these vessels survived the pneumonectomy.

The experiments herein reported suggest that the bronchial arteries play an important, if not indispensable, role in lung function. Failure of the animals to survive using only a lung with the bronchial arteries divided implies the importance of this arterial system. The anatomic distribution of the bronchial arteries in the dog (Virchow,[14] Zuckerkandl,[15] Konaschko[8]) is such that these arteries can be expected to perform a vital role supplying oxygen to the bronchi. Verloop,[13] furthermore, contends, in the human, that bronchial arteries nourish the bronchial wall, the adventitia of the pulmonary artery and veins, and the visceral pleura. He also contends that the bronchial arterial blood is essential to the nervi pulmonalis, which usually lie next to the arteriae bronchiales. Boyden[2] agrees with Verloop's remarks. Thus, there are several points at which respiratory function might be impaired by ablation of the bronchial arteries. The detailed mechanism which played a role in these experiments is not elucidated and remains for further study. In any case, whatever the particular mechanism may be, whether by impaired ciliary action, abnormal mucus production, disturbed innervation and motor activity,

or from other causes, these experiments suggest that bronchial artery ligation leads to changes which prevent adequate respiration. While transplantation of organs awaits solution of the problem of immune reactions, it might be helpful to solve, if possible, other technical difficulties. In the case of lung transplantation it would appear desirable to include with the lung transplant an adjacent section of aorta with intact bronchial arteries.

SUMMARY

Experiments have been performed on dogs, involving temporary and permanent interruption of the bronchial and hilar adventitial arteries and temporary pulmonary artery interruption to one lung. Contralateral pneumonectomy was performed in order to provide a physiologic test under these circumstances. Temporary pulmonary artery occlusion to one side as well as temporary bronchial artery occlusion were well tolerated. After either procedure contralateral pneumonectomy usually was survived. Permanent interruption of the bronchial and hilar adventitial arteries ordinarily did not permit survival after contralateral pneumonectomy.

CONCLUSIONS

Under the conditions of these experiments, temporary occlusion of the pulmonary artery of one lung for a period of one hour appears to have no effect upon the subsequent function of that lung.

Simultaneous occlusion of the pulmonary artery and the bronchial arteries for periods up to 30 minutes likewise does not affect lung function adversely.

When the bronchial arteries and the hilar adventitial arteries are divided, the survival rate following contralateral pneumonectomy is strikingly lowered.

It is suggested that the failure of experimental autologous lung transplantation may be related, in part, to disruption of the bronchial artery and hilar adventitial circulation.

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SIMPLIFIED METHOD FOR ESOPHAGEAL HIATAL HERNIORRHAPHY

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(From the University of Rochester School of Medicine and Dentistry)

FOR clarity of anatomic detail and ease of observance of the principles of repair, the transthoracic approach to esophageal hiatal herniorrhaphy is superior to the abdominal route. The noteworthy contributions of Harrington, Sweet, and Allison to an understanding of the structural peculiarities of the region are well known. In spite of the brilliant successes reported by Harrington,[2] employing the transabdominal technique, it seems that in the future uniformly superior results will be achieved by the occasional operator in this region, utilizing the transthoracic route.

It is the purpose of this report to suggest an improved method for handling the esophagophrenic ligament which we believe to be fundamental in accomplishing permanent hernia repair. Sweet[4] uses longitudinal or circumferentially placed plication sutures to obliterate the hernial sac and shorten the esophagophrenic ligament (Fig. 1). Allison[1] excises a transverse strip of ligament and sutures the cut edge to the under surface of the diaphragm (Fig. 2). Madden[3] subtends the importance of the ligament but in effect stitches it to the superior surface of the diaphragm at the hiatal margin as a final step in his repair (Fig. 3).

A brief résumé of the regional anatomy is included to facilitate discussion (Fig. 4). The problem to be dealt with in sliding hiatal hernia is the anteriorly placed peritoneal sac. The cephalad protrusion of this sac and its contents causes a variable amount of stretching of the structures reflected from the lower esophagus to the diaphragm at the hiatal margins. These structures are the parietal pleura and the esophagophrenic ligament. We believe the latter to be a tissue of some strength and integrity, the proper handling of which is vital to permanent repair. Careful dissection at the time of operation has convinced us that fascial contributions to the esophagophrenic ligament are made from the superior as well as the inferior surface of the diaphragm as illustrated in Fig. 4. As a result the repair to the described is designed to take advantage of this conviction.

OPERATIVE TECHNIQUE

Via the transthoracic approach, with the left lung retracted superiorly, the deranged anatomy is clearly seen in profile. This circumstance does not occur when the abdominal route is used. The left index and middle fingers are inserted into the hernial sac via a 2-inch radial incision in the diaphragm. This

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Fig. 1.

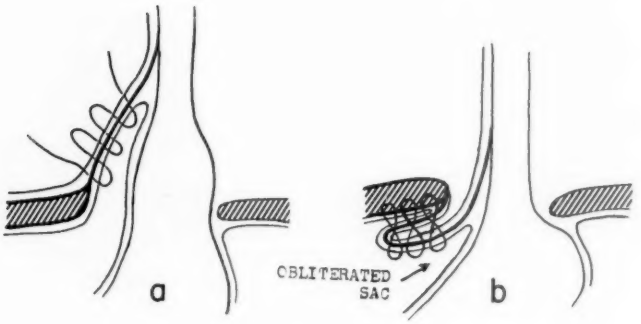

Fig. 2.

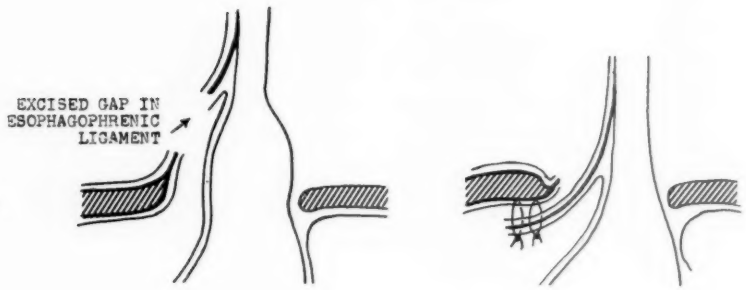

Fig. 3.

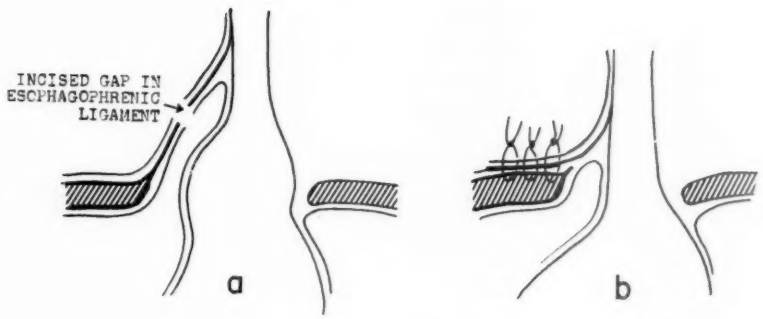

Fig. 4.

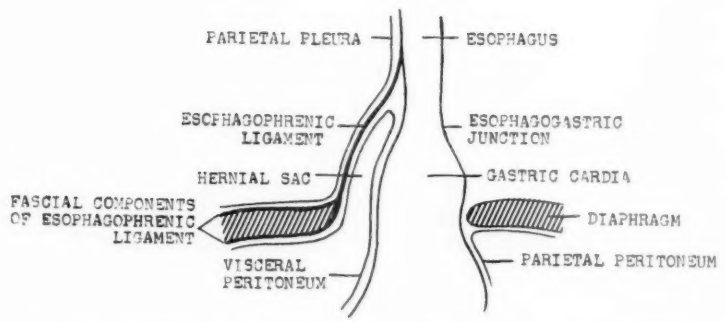

Fig. 1.—Sweet's method of imbricating the esophagophrenic ligament.

Fig. 2.—Allison's method of suturing the esophagophrenic ligament to the under surface of the diaphragm.

Fig. 3.—Madden's technique of suturing the esophogophrenic ligament to the superior surface of the diaphragm.

Fig. 4.—Diagram illustrating the regional anatomy encountered in sliding esophageal hiatal hernia.

maneuver accomplishes 2 objectives. One, it allows the operator to excise safely an appropriately dimensioned strip of stretched out esophagophrenic ligament and, two, it permits easy reduction of the stomach into the infradiaphragmatic position. If the hernia is relatively small it may be appropriate to merely incise the ligament. However, moderate to large-sized hernias elongate the ligament to such an extent that excision will be needed to eliminate redundancy. In either circumstance, it is advised that a 2 cm. proximal cuff of esophagophrenic ligament be retained to facilitate secure suture placement.

Employing 0-0 silk, the needle is passed successively through the diaphragm from above downward and the hiatus in a cephalad direction is mattressed to the proximal esophagophrenic ligament, the hiatus caudally, and the diaphragm from inferior to superior surface to terminate 5 mm. from the other strand of the suture. The sutures are not tied until all have been placed, usually 4 to 6 in number (Fig. 5).

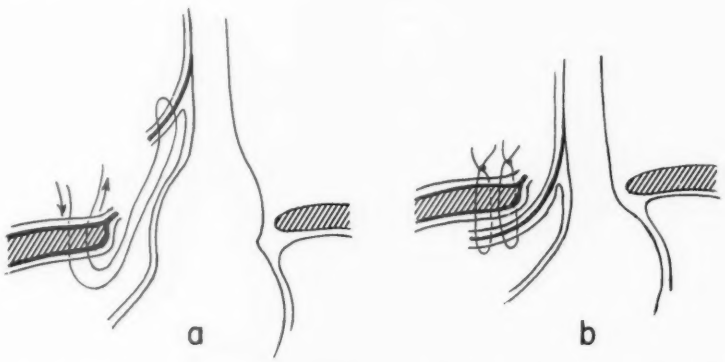

Fig. 5.—Our innovation for handling the esophagophrenic ligament as described in the text.

With the hernia thus reduced the muscular crural limbs are approximated employing simple interrupted 2-0 silk sutures. If feasible this should be done in the vertical plane posterior to the esophagus. However, as pointed out by Madden, the attenuation of the crural muscles may be in a horizontal plane and tensionless approximation is best achieved in this axis. The objective to be obtained in this segment of the repair is to construct a hiatus that will admit the index finger and esophagus.

COMMENTS

Since adopting this method of repair we have operated upon 5 patients with sliding esophageal hiatal hernia. In only one individual was it necessary to excise a strip of esophagophrenic ligament because of the large size of the hernia and its attendant redundancy. We have been impressed by the facility with which the sutures can be placed. In addition, the expedient of passing sutures through the diaphragm has provided an extra facial buttress against the potentially disrupting stresses inherent in this naturally mobile region. Finally, of the various methods of repair, we have felt this to be the most satisfactory in very adequately reducing the herniated stomach.

SUMMARY

1. A simplified method is described for dealing with the esophagophrenic ligament in the repair of esophageal hiatal hernia.

2. A vote is rendered for the use of the transthoracic approach to hiatal herniorrhaphy.

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Editorial

CONDUCTED BY I. S. RAVDIN, M.D.

Medical Education Week

For the third successive year, Medical Education Week has been observed; this year from April 20 through 26. The organizations supporting this project are: The Association of American Medical Colleges, the American Medical Association, the American Medical Education Foundation, the National Fund for Medical Education, Student American Medical Association, and the Woman's Auxiliary to the American Medical Association. This week provides the medical profession as a whole, and surgeons in particular, the opportunity to tell the public the story of the progress and achievements which have been made not only in our medical schools, but in the training programs which follow graduation from the medical school and the internship. It provides the opportunity to inform the American public that nowhere in the world does the medical student obtain better training than in this country. It provides us, too, with the opportunity to help the public understand more clearly than they do now the problems concerned with adequate medical education and the necessity of finding solutions to those problems which concern us and which remain, at present, unsolved.

Medical Education Week provides the opportunity for joint public education by the medical schools, the medical profession, and their allies. The public should understand that while in 1900 the three commonest causes of death in this country were tuberculosis, pneumonia, and the infantile diarrheas, at present the two commonest causes of death are cardiovascular disease and cancer. Intensive research is being carried on in both of these important areas with the hope that adequate solutions can be found for the devastating loss of life which is now associated with these disorders. In every important area of medical and surgical effort, research goes on to the end that we shall know more about these disorders and find solutions for their cure.

The public should know more about the cost of medical education, and realize the importance of providing more adequate financial support for training doctors and specialists. The President has recently indicated that in this area private philanthropy is of the greatest importance.

There are now 83 approved medical schools in the United States. Of these, 79 are conducting full 4-year programs, while 4 are conducting 2-year basic medical programs. Two additional schools have established completely new 4-year programs but will not be eligible for approval until their first classes graduate in 1960. Another 4-year school is scheduled to open in 1959.

With the population increase in this country of nearly 3 million people each year, there must be provided financial support for additional medical schools if the medical profession is to offer the very highest standard of medical care. The graduates of our medical schools have increased from 4,565 in 1930 to 6,796 in 1957. Modern medical training requires small groups of students and a sufficient number of hospital and clinic patients for careful student observation and study. While it is possible that some of the existing medical schools may find it necessary to accept additional students, it is generally agreed that the need for additional physicians cannot be met completely by such a program. New schools must be established, but in order to accomplish this, we shall need more financial help than ever before. Medical Education Week provides the opportunity to present this problem to the American public.

—I. S. Ravdin

Reappraisal

CONDUCTED BY CLARENCE DENNIS, M.D. ASSISTED BY ALFRED HURWITZ, M.D.

RE-EVALUATION OF LIGATION OF THE HEPATIC ARTERY FOR THE TREATMENT OF COMPLICATIONS FOLLOWING INTRAHEPATIC DISEASE

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LIGATION of the hepatic and splenic arteries for the complications of hemorrhage and ascites secondary to Laennec's cirrhosis was first performed in 1947. Since then many patients have been subjected to this procedure by us and others with mixed results. In 1953, we reviewed 23 personal cases operated upon with a total mortality to date of 30 per cent. Since 1953, no further cases have been added for bleeding from esophageal varices, because experience in the first 23 patients had shown that (1) no real decrease in portal venous pressure had been obtained by ligation of the hepatic and splenic arteries and (2) several patients continued to have recurrent hemorrhages after ligation. The operation is still recommended, however, for patients with ascites due to Laennec's cirrhosis (who had not responded to medical management), angiomata of the liver, arteriovenous fistula or aneurysm of the hepatic artery, and hepatic metastases. Good results have been obtained in each of these conditions with a mortality of approximately 16 per cent. In fact, the first patient, with typical Laennec's cirrhosis proved by biopsy, was operated upon in 1947 and is still alive and well without ascites and with normal liver function studies.

The good results obtained in cases of ascites are due we believe to a decrease in total hepatic blood flow rather than to a decrease in portal venous pressure. As anatomic studies have shown, the extrahepatic arterial anastomoses in the region of the porta hepatis vary greatly in individuals and this probably accounts for the reported differences in results. Unfortunately, reports of single cases or of small series, as have been numerous in the literature, are not representative of the true value of this procedure. In our series, no instance of gross infarction of the liver occurred following hepatic arterial ligation. In other reports various operators have obtained quite striking results, not only in ascites, but also in cases of patients desperately ill from hemorrhage whose condition was not thought to be sufficiently good to withstand portacaval shunt.

The immediate mortality following ligation of the hepatic artery in our series was thought to be due more to progression of the fundamental disease

than to the operation itself. It is our present feeling that ligation of the common hepatic artery distal to the gastroduodenal artery combined with ligation of the splenic and left gastric arteries is the operation of choice in patients with intractable wasting ascites despite adherence to a proper medical regimen, the mortality not being prohibitively high. Portacaval or splenorenal shunts are probably the operations to be preferred for bleeding esophageal varices due to portal hypertension.

REAPPRAISAL OF SIDE-TO-SIDE AND END-TO-SIDE INTESTINAL ANASTOMOSES

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EXPERIMENTAL evidence has revealed that side-to-side and end-to-side anastomoses may be followed by untoward sequelae. Pearse[8] showed that in the dog, the longer the blind loop, the more likely the occurrence of distention of the loop, infection of the bowel wall, weakness, lassitude, diarrhea, and perforation. He also demonstrated the fact that if the blind loop was designed so that peristalsis emptied it readily, no untoward sequelae developed. If, on the other hand, the blind loop was placed in a dependent position so that it became a trap for the accumulation of intestinal contents, then the complication rate was high. Cameron and co-workers[3] were able to produce macrocytic anemia in rats after the production of blind loops. The development of the anemia was enhanced by placing the loop in a dependent position so that it could be filled with stagnant, undigested material. This complication was most likely to occur if the upper or middle third of the small intestine was selected. Brown[2] showed that, in pigs, diarrhea and anemia were not likely to occur even after removal of part or almost all of the small intestine. Short-circuiting of part of the small bowel had no deleterious effect, but short-circuiting of almost the entire small bowel was followed by diarrhea and severe microcytic anemia.

There are several articles in the surgical literature which emphasize the untoward sequelae that follow side-to-side anastomosis. Estes and associates[6] reported 2 cases of ulcerative enterocolitis in the side-tracked loop. They stated that "entero-anastomosis for intestinal obstruction must be looked upon as a possible first-stage operation of which resection of the obstructed loops may be required as a second operation."

Clawson[4] presented a case illustrating the complications of dilatation, ulceration, and macrocytic anemia occurring 10 years after a side-to-side anastomosis in the terminal ileum. The condition was corrected completely after the anastomosis was resected and an end-to-end anastomosis performed.

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Halsted[7] studied the pathogenesis of macrocytic anemia in 3 cases. One patient had a fistula between loops of small bowel. The second had an end-to-side anastomosis between ileum and hepatic flexure with the production of a blind loop in the right colon and the third had a side-to-side anastomosis following obstruction secondary to postappendectomy adhesions. In all 3 patients absorption of radioactive vitamin B_{12} administered orally was shown to be impaired. Administration of the intrinsic factor was not followed by an amelioration of the macrocytic anemia. The ingestion of Achromycin resulted in a markedly increased absorption of vitamin B_{12}. In the third case, 91 per cent of the radioactive B_{12} given by mouth was recovered in the stools. After the administration of 2 Gm. of Achromycin daily, only 25 per cent was excreted and the macrocytic anemia improved. Two weeks after Achromycin was stopped, 73 per cent was recovered in the stools. He implicated bacterial infection as the etiologic factor in the production of the macrocytic anemia.

Benson[1] reported only 4 survivals of 8 newborn infants with intestinal atresia and stenosis of the jejunum and ileum who had side-to-side anastomosis performed without resection. Of the 4 survivals, 2 infants developed a blind loop syndrome characterized by diarrhea, abdominal cramps, and weight loss 11 and 23 months after operation, respectively. Following resection of the distended blind pouch and the anastomosis, an end-to-end anastomosis was performed with gratifying results. Swenson[9] has advocated the use of the end-to-end anastomosis in infants and children. This procedure was accomplished despite the fact that over one-half of the infants were under 6 months old. He concluded that end-to-end anastomosis had proved successful with a satisfactory mortality rate. There were only 3 postoperative deaths in a series of 32 patients and no significant complications in the survivors. Dennis[5] described a safe, simple, one-layer silk, end-to-end anastomosis in the treatment of gangrenous and nonreducible intussusceptions in children.

During the past year side-to-side anastomoses were performed in 2 instances at Maimonides Hospital; one because of obstruction secondary to a stenosis occurring after reduction of an umbilical hernia and the other because of obstruction associated with an area of chronic inflammation in the jejunum following a previous appendectomy. The first patient continued to have cramps and to run a low-grade fever for 5 months when a 60 cm. resection of the loop was performed and an end-to-end anastomosis done. Following this operation the patient has enjoyed good health. The second patient had complete relief of abdominal cramps, weakness, loss of weight, intestinal bleeding, and anemia after resection of the previous anastomosis together with the side-tracked loop. Both specimens showed marked thickening of the bowel wall and areas of ulceration in the isolated loop and both were diagnosed as acute and chronic regional enteritis.

There seems to be little reason for perfoming any type of anastomosis other than an end-to-end anastomosis. If resection is not feasible, for instance, obstruction secondary to an inoperable carcinoma, division of the

intestine proximal and distal to the matted bowel with exteriorization of the loops as mucous fistulas can be performed with end-to-end anastomosis of the proximal and distal intestine. Side-to-side anastomosis for the treatment of this condition would result in the formation of a long side-tracked loop with a high incidence of stagnation and ulceration. In conclusion, end-to-end anastomosis is the most physiologic operation and the procedure of choice when an anastomosis of the small or large bowel is indicated.

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FOLLOW-UP REPORT ON TRANSDUODENAL SPHINCTEROTOMY FOR RELAPSING PANCREATITIS

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IN 1953 we submitted a report on transduodenal sphincterotomy for relapsing pancreatitis. It was noted at the time that the follow-up period was too short to permit valid conclusions as to the effectiveness of the procedure. Since all cases in the original report are now at least 5 years postoperative, the results may now be critically examined (Table I).

Among the results reported as excellent, 2 patients died of other causes, one 3 and the other 4 years after operation, neither having had any further attacks of pancreatitis. In addition, one patient had an attack of severe pain when the T tube was removed but no attacks in the next 7 years. Another patient in this group had an attack of pain lasting 14 minutes following an injection of morphine but no other evidence of pancreatitis in 5½ years.

Cases were classified as good when they had no definite episodes of pancreatitis but had intermittent epigastric distress of some sort.

TABLE I

Total cases reported	23
Lost to follow-up	5
Available for analysis	18
Results	
Excellent	9
Good	4
Fair	2
Failures	3

Cases were classified as fair when infrequent attacks occurred, in addition to indigestion.

Failures were those in which the procedure did not alter the patient's former symptomatology.

We have now performed 63 transduodenal sphincterotomies, with one death due to a duodenal fistula and another to a postoperative coronary thrombosis at home. There have been no cases of postoperative cholangitis, and the morbidity in general has not surpassed that of cholecystectomy with choledochotomy.

Our present technique is essentially as described originally, with 2 exceptions. We no longer bring the long arm of the T tube through the sphincter, and it is removed usually in 7 to 10 days. In addition, we often use a small Foley catheter drawn down the duct from below, gently inflating the bag above the sphincter, so that the latter may be elevated easily into the wound.

On the basis of our experience, we feel that sphincterotomy is of considerable value in the management of relapsing pancreatitis. The procedure should not be carried out unless the diagnosis can be established by history, physical examination, and pertinent laboratory data, including elevated amylase or lipase levels. Our poor results in the reported series were largely in patients whose diagnosis had not been thoroughly proved.

In the presence of a normally functioning gall bladder, we advocate intensive medical and/or psychiatric treatment before resorting to surgery, since emotional factors can play a major etiologic role.

When the gall bladder is pathologic and the pancreatic component of the clinical picture seems mild, we, as a rule, perform only cholecystectomy and choledochotomy if indicated, reserving sphincterotomy for a second procedure, if necessary. If the symptoms of pancreatitis are dominant, however, sphincterotomy is performed at the time of cholecystectomy.

If one adheres to such a conservative approach to the management of this difficult problem, we believe the end results will prove eminently satisfactory.

Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

GUILLAUME DUPUYTREN AND DUPUYTREN'S FRACTURE

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"Le repos, c'est le mort."

ONE of Dupuytren's contemporaries has left us a series of delightful sketches of the leading medical personalities of his day. Before taking up Dupuytren, he prefaces his remarks: "If I could have avoided speaking of M. Dupuytren, it would have been a great relief to me, for I find myself in a very uncomfortable embarrassment. I am almost sure to leave all parties dissatisfied." About no other surgeon have so many violently opposing opinions been expressed by his associates and perpetuated by his biographers. Many of his detractors are remembered today only because of their vitriolic epigrams directed at him. Perhaps the most widely known is that Dupuytren was the greatest of surgeons, the meanest of men. To understand the depth of this feeling today, one need only know that Percy, long surgeon-in-chief of Napoleon's armies, could never forget that Dupuytren was deferred from the draft and excused from military service on the plea of the Faculty of Medicine that his services were essential and that, while the titles of most of his associates stemmed from the Emperor Napoleon, he was made a Baron by Louis XVIII, a Bourbon.

Dupuytren's name has been applied as an eponym to at least 12 diseases, operations, or instruments, the most widely used being, of course, Dupuytren's contracture. Only rarely is reference made to Dupuytren's fracture. The description of this injury is not found in a brief case report of a single patient with a new variety of ankle fracture, but rather consists of a long and learned treatise. There is a thorough review of the history of the treatment of ankle fractures and of the normal anatomy and function of the ankle joint. Of special interest is the description of experimental fractures produced in cadavers to elucidate the mechanism of injury. The discussion of the clinical history, signs, symptoms, and complications is comprehensive. To all of this is added a description of a new method of treating these fractures which is based upon the principles demonstrated previously, with a report of the use

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of this method in 207 patients with the injury. Fractures of this type had been described before by Pott and others, but Dupuytren's eponym is deservedly attached to the fracture because of the classic manner of his descripton, not only of the fracture, but of a successful method of treatment. Dupuytren himself refers generously to the work of his predecessors and was under no misapprehension that he was describing an injury previously unrecognized.

Dupuytren's fracture has been defined by Bonnin,[2] a critical commentator upon ankle injuries, as: "a fracture of the fibula above the syndesmosis, but below the centre of the fibula, with partial diastasis." Two varieties are distinguished: a "high Dupuytren," a fracture of the fibula 2½ to 3 inches above the syndesmosis due to flexion-rotation strain, an external rotation fracture; and a "low Dupuytren," a fracture of the fibula within an inch of the syndesmosis, of a similar type, in which abduction violence perhaps predominates. The "high Dupuytren" fracture sometimes also bears the eponym of Hugier (Fig. 1).

These fractures comprised one-third of all of the fractures of the leg seen in Dupuytren's clinic. The results of the usual forms of treatment were very unsatisfactory. He felt that although Pott and others had learned how to reduce the fractures the methods of maintaining the reduction were not adequate. Dupuytren's apparatus for maintaining reduction consisted of (1) a wedge-shaped cushion about two-thirds filled with bran or cotton and of sufficient length to extend from the internal malleolus to the knee, (2) a wooden splint about 2 feet long and 3 inches wide, and (3) 2 roller bandages 4 or 5 yards long. The fracture was reduced by manipulation with inversion of the foot. The wedge-shaped cushion, base downward, was applied to the inner side of the leg. The splint was then applied to the cushion and extended below the sole of the foot. These were then firmly held in place by the roller bandages applied from just below the knee to a short distance above the fracture, and thence around the foot and instep in a figure-of-eight to maintain the inversion of the foot (Fig. 2).

Dupuytren's interest in fractures was not confined to those about the ankle. The Hotel Dieu received a continuing stream of patients injured in the streets of Paris. Dupuytren recognized the value of good first-aid and deplored the zeal of the uninformed bystander whose ministrations so frequently complicated a simple injury. An intensely practical man, he designated the first floor of the Hotel Dieu for the reception of patients with fractures to avoid having to move them up and down the narrow stairways. Dupuytren was a strong advocate of the practice of Pott, who used the semiflexed position in treating fractures of the extremities in order to obtain the maximum degree of muscular relaxation. This was contrary to the method of treating fractures in extension then well established in France. The *Leçons Orales* contains many comments on fractures in children and on pathologic fractures due to bone disease. The problem of nonunion led him to become interested in the normal process of fracture healing. Dupuytren was the first to differentiate between provisional callus, forming quickly during the first month of healing, and definitive callus, which produced final solid union of the fracture after many months.

Dupuytren was born Oct. 5, 1777, in Pierre-Buffiere, a small town in central France just south of Limoges. His father was an attorney of limited means and only because of the interest of a cavalry officer stationed in the town was Dupuytren enabled to go to Paris for his schooling. The grinding poverty and privation of his student days cast the shadows of avariciousness and parsimony into his later years.

Fig. 1.

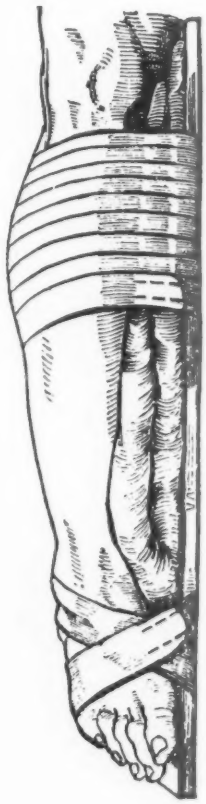

Fig. 2.

Fig. 1.—An example of Dupuytren's fracture taken from Nelaton, Elements de pathologie chirurgicale, Paris, 1874.

Fig. 2.—Dupuytren's method of splinting his fracture with the foot maintained in inversion and slight equinus.

With absolute faith in his own ability, Dupuytren made work his religion. In a fiercely competitive system he rose in 20 years from the position of prosector of anatomy to become Chief Surgeon of the Hotel Dieu. Born in poverty, he was able to offer magnanimously the deposed Charles X one million francs from his personal fortune at 53. "Had not *Monsieur* Dupuytren been compelled from poverty to trim his students' lamp with oil from the dissecting room, he never would have succeeded in becoming *Monsieur le Baron* Dupuytren" (Fig. 3).

As one Frenchman has aptly put it: "Modesty is not a defect of French character." Dupuytren's era was the high-water mark of French surgery, and

his Paris, the center of the medical world. Amid a galaxy of brilliant minds he would not acknowledge a superior, but reigned alone, coldly critical of all those about him. He had no friends among his medical colleagues. He was devoted to the care of his patients and never shirked his responsibilities to the inmates of the Hotel Dieu. Of the many crimes of which he was accused, no one ever suggested that he put his private interest above that of the meanest of his patients. His funeral cortege was interrupted as it made its way to the cemetery by crowds of workmen who took the coffin on their shoulders and bore it part of the distance. Among them was the coachman upon whom Dupuytren had performed the first successful resection of the mandible for a tumor many years before. They were his friends.

Fig. 3.—Guillaume Dupuytren (1777-1835).

As a surgical technician Dupuytren was surpassed by a few of his contemporaries. As a surgeon, he reigned supreme. He was conservative in his indications for operation. "We should never lose sight of the importance of preserving whilst we are curing." Once operation was decided upon, every effort was made to get the patient into the best possible condition. The preoperative and postoperative care of his patients was given great attention. Before performing an unusual procedure, Dupuytren would rehearse his technique upon cadavers. Not a speedy technician—"Rapidity in operating is a poor compensation for the risk it often entails"—he was systematic and carefully organized, never unnerved by the unexpected, always resourceful in any

exigency. He was the first to ligate the subclavian and external iliac arteries successfully, to treat torticollis by subcutaneous tenotomy of the sternocleidomastoid, and to excise successfully the mandible.

The conditions under which the surgeons of this era worked would chill the blood of any surgeon today. Not only was there neither anesthesia nor antisepsis, but crowding, poor hygiene, filth, and malnutrition were the rule. A visitor to the Hotel Dieu describes an emergency herniotomy performed by Dupuytren on an 80-year-old woman whose hernia had been incarcerated for 9 days. The operation was performed at night without moving the patient from her bed in the ward. Since it was night, "so few pupils were present, that there was hardly a sufficient number of candle-holders and assistants. I never saw it [the operation] performed with less hurry, nor with more speed."

Dupuytren multiplied the fruits of his restless activity by the efficiency with which he organized his work. His schedule was rigid and unvaried. He recognized the importance of good medical records: the history, the physical findings during the course of the disease, and the description of the surgical or autopsy specimens. He had his own record librarian at the Hotel Dieu to keep tract of the clinical material. This enabled him to base his conclusions regarding diagnosis and treatment, not on the mirage of clinical impression, but upon the complete records of all of his patients.

The advantage of this system is seen in his discussion of burns in which he reviews the results of the treatment of all of the burned patients admitted to the Hotel Dieu during one year. There were 50 patients and a mortality rate of 13.6 per cent. The patients were classified as to age, sex, size and location of the burned area, and cause of death. In addition the burns were classified as to degree, this concept having been introduced by Dupuytren. His original classification included 6 degrees, the first 3 of which are essentially those used in classifying burns today.

Dupuytren had tried many methods of dealing with colostomies, and after a large number of experiments on dogs finally developed his enterotome for crushing the spur. It was used on a patient for the first time in 1816. In 1824, Dupuytren was able to report upon its use in 41 patients. In 29 of these there was a complete cure; in 9, partial success with a residual fistula; and, in 3 death from peritonitis. His demonstration of the union of segments of bowel by the apposition of their serosal surfaces is said to have suggested to Lembert a method of suturing the bowel.

Dupuytren was not always right, unfortunately, and his incorrect opinions were supported by the same weight of authority as his correct ones. He believed and taught that the acute suppurative processes arising in the right lower quadrant began in the cecum. He did not grasp the concept of acute appendicitis although his two countrymen, Louyer-Villermay and Melier, had separately reported typical cases of appendicitis and had indicated the appendix as the seat of the disease. Dupuytren's insistance on the importance of the cecum in this condition retarded the general recognition of appendicitis as a disease for years.

At one time Dupuytren was asked by the Paris police to help in the identification of a badly decomposed body of a man, brutally murdered, which had been found in a sack. Examining the body, he discovered that the victim had a congenital dislocation of the hip. Inquiry revealed that a missing person being sought had had a limp and other typical signs of such a deformity. This led to positive identification of the body.

Dupuytren had more than a passing knowledge of congenital dislocations of the hip. He had examined at least 30 patients with this condition, 26 women and 4 men. He described all of the physical signs associated with the deformity. In presenting a family history of 3 generations with this condition, it is clear that he recognized the possibility of its familial nature. Most important of all, he gave the first clear description of the pathologic anatomy of congenital dislocation of the hip. His enumeration of the various theories of etiology is essentially the same as we have today.

In all of his work he introduces numerical and statistical data of this type which gives his writing a very modern air when compared with that of most of his contemporaries. Perhaps this helps to explain why Dupuytren, although acquainted with the medical literature of his day, was little impressed by it. He preferred to base his conclusions upon his own experience, saying: "How many considerations founded on theory disappear at the bedside."

As a teacher, Dupuytren attracted large numbers of students to his ward rounds and lectures. As many as 1,200 students, an incredible number, attended some of his lectures on hernia. He was especially brilliant as a diagnostician, always ready with the essential question in the history, keenly aware of the physical signs of disease. The essence of his clinical lectures was collected and published by two of his students. He, himself, never published a systematic work on surgery as a whole, but these lectures, the *Leçons Orales,* provide an excellent substitute, ranging widely through a great variety of subjects.

Oliver Wendell Holmes[9] as a visiting student in Paris has left us his impression of Dupuytren the teacher. "I saw him. . . : a square solid man with a high-domed head, oracular in his utterance, indifferent to those around him, sometimes, it was said, very rough with them. He spoke in low even tones, with a quiet fluency, and was listened to with that hush of rapt attention which I have hardly seen in any circle of listeners unless when such men as ex-president John Quincy Adams or Daniel Webster were the speakers. I do not think that Dupuytren has left a record which explains his influence, but in point of fact he dominated those around him in a remarkable manner. You must have all witnessed something of the same kind. The personal presence of some men carries command with it, and their accents silence the crowd around them, when the same words from other lips might fall comparatively unheeded."

Dupuytren had said that at age 60 he would retire. No one believed this, and it is doubtful if he did himself. His attitude toward his work was too well known. Sir Astley Cooper had entertained him at his country estate in England to which Cooper had retired. During a tour of the park, Sir Astley had commented: "In London I would die of over work; here, I shall die of

boredom." Dupuytren replied: "In your place, I would return to London." Unfortunately he never had to make this decision for himself. On Nov. 16, 1833, while lecturing in the Hotel Dieu, he was stricken with a hemiperesis and a facial palsy and finished his lecture with difficulty. He was unable to resume his duties. A visit to Italy failed to recoup his health. He returned to Paris to die. A chronic pleurisy developed into an empyema and his student Sanson proposed drainage. Dupuytren refused, preferring to die by the hand of God than by the hand of a surgeon. The day of his death he requested his servant to read the newspapers to him so that he could take the latest news of this world into the next. He died on Feb. 8, 1835.

Shortly before his death, Dupuytren had discussed with Orfila the possibility of leaving funds to the University for the endowment of a chair of pathologic anatomy, suggesting Cruveilhier for the position. As an alternative, the funds could be used to establish a museum of pathologic anatomy. After his death, the government provided the funds to establish the chair of pathologic anatomy, and in November, 1835, Le musée Dupuytren was opened to the public.

It is interesting to note that during 1835 the positions held by Dupuytren were passed on, not to one man, but to three; Roux taking his service at the Hotel Dieu, Sanson succeeding to his chair of clinical surgery, and Breschet, his chair at the Academie de Médecine.

To relate all of the anecdotes, to probe all of the facets of this complex personality, even to list all of his contributions to our knowledge of surgery is to attempt too much. It is sufficient to say that the use of Dupuytren's eponym perpetuates the memory of the greatest French surgeon of the nineteenth century and perhaps since Paré himself.

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Book Reviews

CONDUCTED BY J. GARROTT ALLEN, M. D.

Bone Tumors. General Aspect and an Analysis of 2,276 Cases. Charles C. Dahlin. Springfield, Ill., 1957, Charles C Thomas. Pp. 219. $11.50.

This atlas represents a 9-year review by Dr. Dahlin and others at the Mayo Foundation of more than 2,000 consecutive and unselected bone tumors. The availability of follow-up records has made possible the correlation of the clinical features with the gross and microscopic. These are generously included in the form of age, sex, and skeletal distribution charts, roentgenograms, photomicrographs, and photographs of the surgical specimens. These illustrations are of high quality and are abundantly employed. The concise text expands upon the clinical features, describes the gross and microscopic pathologic picture, and outlines the generally accepted modes of treatment and prognosis. The bibliography is very limited but generally includes well-respected contributions to the field of bone pathology.

Since no atlas is complete without a table of classification of tumors of bone, Dr. Dahlin has provided one similar to that foreworded by Lichtenstein for primary neoplasms of bone. Herein lie recognized sources of controversy, such as, Giant osteoid osteoma, fibroma of bone, and Ewing's tumor. In conclusion, the author discusses several non-neoplastic diseases of bone to be differentiated from primary bone neoplasms. This book should prove useful to the student of orthopedic surgery, especially during his residency period and early years of clinical practice.

—E. Byron O'Neill

Hypophysectomy. Edited by O. H. Pearson. Springfield, Ill., 1957, Charles C Thomas. Pp. 156, 24 tables. $5.00.

This represents a collection of the papers presented and the succeeding discussion which took place at meetings held at the Sloan-Kettering Institute, Memorial Center, New York, in 1956. Gathered together at this meeting were many of the leading surgeons, radiotherapists, and endocrinologists in the field of hypophysectomy.

Most of the material presented is oriented around the role of hypophysectomy in the management of cancer of the breast, but brief mention is made of its value in prostatic cancer and in diabetes mellitus when there are vascular complications, and its lack of effect in other types of cancer.

The series of cases reported, with two exceptions, are too small to be of statistical value. But together, they represent a wealth of material and therefore deserve careful study. A comparison of clinical results, complications, mortality rate, and extent of destruction or removal obtained by one route or method of destruction as against another is very illuminating.

The impression is gained that in spite of the high degree of technical excellence which has already been developed in the surgical removal of the gland, the mortality and complication rate is higher than with radioisotope or proton beam destruction, and it is to these latter methods, which at present give uncertain results, that one must look for further advancement in this field.

It is readily apparent that some major problems still beset this field and among these are the preoperative estimate of the benefit the patient is likely to gain from the

procedure, the duration of remission or regression if it is obtained, and the necessity to devise a reliable postoperative test which would indicate the degree of completeness of destruction or removal of the hypophysis.

For anyone working in the field of cancer or endocrinology, this volume of 156 pages, 24 tables, and limited bibliography makes valuable reading.

—William M. S. Ironside

Lumbar Puncture and Spinal Analgesia. Sir Robert Macintosh. Ed. 2, Baltimore, 1957, Williams and Wilkins Company. $6.00.

The second edition of this monograph is essentially identical to the first printing published in 1951, and the author himself does not claim any major changes.

The emphasis—almost half of the book—is on basic anatomic considerations. Superb illustrations together with clear descriptions relating techniques and fallacies of lumbar puncture and administration of anesthetic agents to topographic anatomy and physiology are responsible for the value and popularity of Macintosh's work.

One definite improvement of the new edition is the addition to the table on page 117 of the relationship of the specific gravity of cerebral spinal fluid to Nupercaine solution 1:1500 and water, since the relative weight of spinal fluid and anesthetic agent are of primary clinical importance. Comparative values of other frequently employed anesthetic solutions would have further increased the usefulness of this table.

Fig. 85, however, showing spinal needle directors, is less complete and the instruments are not labeled. This illustration was better in the first edition.

It is regrettable that a chapter on continuous spinal techniques and agents and methods other than Nupercaine 1:1500 were not added to the new edition and that prophylaxis and treatment of complications still are largely limited to "headache."

The bibliography has not been brought up to date.

But for these few drawbacks, the book will and should continue to belong on the bookshelf of every student of anesthesia as well as the accomplished practicing and teaching anesthesiologist.

—Rose Engel

Nursing Care of the Surgical Patient. John Pettit West, Maneleva Wylie Keller, and Elizabeth H. Harmon. Ed. 6. New York, 1957, The Macmillan Company. Pp. 699. $5.75.

Designed primarily for use by basic nursing students, this revised text presents the fundamentals of surgical nursing in clear, concise language and easy-to-read style. The use of technical terminology seems restricted to essentials and the terms are carefully defined. As stated in the preface, "only surgical conditions most commonly encountered are discussed to give the student the fundamentals on which to base her nursing care."

Similar to the earlier edition, the subject matter in this book is organized into 3 units. Unit I, "Introduction to Surgical Nursing," proceeds from a brief overview of the aims of surgical nursing to an equally brief discussion of surgical problems and medical progress. More definitive chapters follow dealing with wounds and repair, infection and inflammation, and tumors and cysts. It is in relation to the chapter on tumors and cysts that the authors develop and correlate nursing responsibilities associated with caring for the patient with cancer.

The second unit, "Fundamental Considerations," presents those aspects of surgical nursing which may be applied to the care of any patient undergoing surgery. No specific relationships to particular surgical conditions or operative procedures are considered in the discussion of electrolyte balance, anesthesia, preoperative and postoperative care, postoperative complications, and care of surgical wounds.

Added to this edition in Unit II are 2 new chapters. One introduces the student to operating room nursing while the other presents the nursing aspects involved in the rehabilitation of the surgical patient.

The content material in Unit III, "Surgical Treatment and Nursing Care," is organized on the basis of individual systems with an additional chapter discussing conditions of the ear, nose, and throat. Diseases common to each system are reviewed in relation to surgical treatment and nursing care.

Liberal use of illustrations throughout the book adds much to the meaning of the material. "Questions for Review" follow each chapter and afford the student a self-testing means for summarizing the subject matter. Supplementary readings at the end of each chapter are listed for the student's further reference.

As stated by the authors this text was intended for use as a guide rather than a sole source.

—Josephine Sana

Peripheral Nerve Regeneration (VA Medical Monograph). Edited by Barnes Woodhall and Gilbert W. Beebe, June 26, 1956. (For sale by Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. Pp. 600.

In the last paragraph of this 600-page book, it is stated that the history of military neurosurgery demonstrates the fact that succeeding generations fail to use the accumulated knowledge of the past. Certainly no future student of peripheral nerve surgery can complain that this knowledge is not now adequately available. In this encyclopedic follow-up of 3,656 World War II injuries, one of its main strengths lies in the ample statistical support for the measures and conclusions adopted. This encyclopedic, statistical approach does, however, make it dull reading, but it is not intended to be an introduction to the subject.

There is a wealth of detail on every possible type of peripheral nerve injury, on optimum time to operate, and on the time not to operate, on the choice of method, and on the results to be expected.

Practically every young surgeon engaged in the treatment of peripheral nerve injuries lacks the volume of experience that will bring perfection to his work and few can afford not to avail themselves of the information that this book contains. Even the more experienced may find a wealth of information on the less common injuries and complications which will repay the effort needed to delve among the minutiae and the statistics.

In short, it is a difficult book to read, but invaluable both for study and for reference.

—John F. Mullan

Selected Writings of Walter E. Dandy. Compiled by Charles E. Troland and Frank J. Otenasek. Springfield, Ill., 1957, Charles C Thomas. Pp. 789. $15.00.

The former residents and friends of Walter Dandy must be thanked for making available to us this selection of his important writings. He was outstanding in a generation of outstanding neurosurgeons and his contributions revolutionized the art. It is difficult for us to appreciate now that before his introduction of roentgenography of the brain, tumors were localized accurately in little over 50 per cent of cases. We can now scarcely imagine performing negative explorations on more than 40 per cent of our patients. His studies of hydrocephalus and his experience in intracranial vascular surgery, to mention but 2 subjects, are likewise monumental, but his interests ranged widely throughout the entire field of neurologic surgery. The editors have given us this breadth in their selection.

As in any active field of knowledge, the opinion of the pioneers will in some instances be challenged and some will eventually prove incorrect, but the foundations they have laid will remain with us. This volume gives us many enduring foundations and in its scope it is, in a way, a history of the development of neurosurgical knowledge and technique during the past generation.

The reputation of the author is such that these writings require no recommendation. They will be found on every neurosurgeon's bookshelf and many of us will be glad to have the lifetime experience of Walter Dandy at our call; and if we should pursue the history and development of our specialty his writings and many lists of references will point the landmarks of our quest.

—John F. Mullan

Calendar of Surgical Meetings

AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 5-8, 1958, Royal York Hotel, Toronto, Ontario, Canada. Secretary, Dr. Robert McLaurin, University of Cincinnati, Cincinnati, Ohio.

AMERICAN ASSOCIATION FOR THE SURGERY OF TRAUMA. *Annual Meeting,* Oct. 2-4, 1958, The Drake Hotel, Chicago, Ill. Acting Secretary, Dr. James K. Stack, 700 N. Michigan Ave., Chicago 11, Ill.

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 16-18, 1958, Statler Hotel, Boston, Mass. Secretary, Dr. H. T. Langston, 1919 West Taylor Street, Chicago 12, Ill.

AMERICAN CANCER SOCIETY. *Annual Meeting,* Oct. 20-21, 1958, Biltmore Hotel, New York City, N. Y. Secretary, Dr. Scott Hill. Subject, cancer of the colon and rectum.

AMERICAN COLLEGE OF SURGEONS. *Clinical Congress,* Oct. 6-10, 1958, The Conrad Hilton, Chicago, Ill. Secretary, Dr. Michael L. Mason, 40 E. Erie St., Chicago, Ill.

THE AMERICAN GOITER ASSOCIATION. *Annual Meeting,* June 17-19, 1958, St. Francis Hotel, San Francisco, Calif. Hotel Reservations must be secured by writing to Goiter Housing Bureau, Room 300, 61 Grove St., San Francisco. Secretary, John C. McClintock, 149½ Washington Ave., Albany 10, N. Y.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 19-21, 1958, The Grove Park, Asheville, N. C. Secretary, Dr. Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* Dec. 2-5, 1958, Leamington Hotel, Minneapolis, Minn. Deadline for submission of abstracts, Aug. 1, 1958. Secretary, Council on Scientific Assembly, Dr. Thomas G. Hull, 535 North Dearborn St., Chicago 10, Ill.

CENTRAL SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 19-21, 1958, Queen Elizabeth Hotel, Montreal, Quebec, Canada. Secretary, Dr. Angus D. McLochlin, Victoria Hospital, London, Ontario, Canada.

THE INTERNATIONAL CARDIOVASCULAR SOCIETY. *North American Chapter,* June 21, 1958, Sir Francis Drake Hotel, San Francisco, Calif. Secretary, Dr. Henry Haimovici, 105 East 90th Street, New York 28, N. Y.

INTERNATIONAL UNION AGAINST CANCER. *Seventh International Cancer Congress,* July 6-12, 1958, London, England. Secretary General, Harold Dorn, National Institute of Health, Bethesda 14, Md.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 3 and 4, 1958, Mount Washington Hotel, Burton Woods, N. H. Deadline for submission of papers, June 1, 1958. Secretary, Dr. Richard Warren, Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 12-14, 1959, Denver, Colo. Secretary, Dr. James D. Hardy, University of Mississippi Medical Center, Jackson, Miss.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 9-11, 1958, Boca Raton Hotel and Club, Boca Raton, Fla. Attendance by invitation of membership only. Secretary, Dr. George G. Finney, 2947 St. Paul St., Baltimore 18, Md.

WESTERN SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 20-22, 1958, Hotel Kahler, Rochester, Minn. Deadline for submission of papers, Sept. 1, 1958. Secretary, John T. Reynolds, M.D., 612 N. Michigan Ave., Chicago 11, Ill.